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THE OPERATIVE TREATMENT OF LESIONS OF THE LOWER EXTREMITIES IN DIABETES MELLITUS*

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The present report is based on 281 operations performed on the lower extremities of patients with diabetes mellitus and covers a seven year period ending Dec. 31, 1929. See figure 1. In order to standardize as many factors as possible, patients operated on by other members of the staff and a large number treated without operation have not been included.

TREATMENT OF THE PATIENT

Medically, these patients have been taken care of by Dr. E. P. Joslin and his associates Drs. H. F. Root, P. White and W. Curtis, or by Dr. F. G. Brigham, his associate Dr. W. Stevens and his former associate Dr. R. R. Wheeler. The patients have remained, throughout, under the direct care of the internist, who has assumed responsibility for all medical problems that arose. It has been his privilege to question the surgical progress of the patient, if response to diabetic treatment was other than that expected; a persistent high level of the blood sugar or an unusual resistance to insulin frequently being the first sign of sepsis in an amputation stump or of undrained pus in a foot. It has been his duty to make operation as safe as possible at any time it was indicated and, subsequently, to safeguard the patient from coma or hypoglycemia.

A patient entering the hospital with a lesion of the foot is seen by the surgeon some time on the day of admission and within a few hours if extensive infection is present. Once the surgeon has seen the lesion, the entire responsibility for its treatment is his. With few exceptions, the time of operation is determined by the condition of the foot rather than by the condition of the patient and rests therefore with the surgeon. In general, operation is done as soon after admission as a definite decision is reached as to the type of operation indicated, sometimes within a few hours, usually within twenty-four. The surgeon, too, must decide on the type of operation to be performed and, if it is amputation, the level at which it should be done. It would be an unwise surgeon, however, who did not freely utilize the store of information his medical confrère

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has available relative to many factors that influence the operative procedure.

CLASSIFICATION OF CASES

In the treatment, as well as in the discussion, of so-called "diabetic gangrene," a definite understanding of the type of lesion under consideration is essential. Our experience has been entirely in accord with that of Coller and Marsh,[1] who in 1925 stressed the importance of proper classification. It has been our custom to consider a given lesion as due

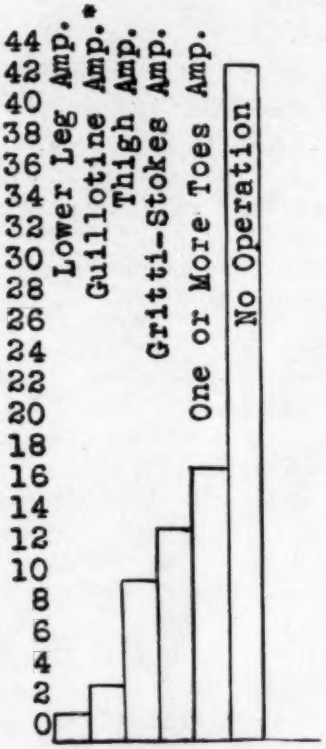

Fig. 1.—A diagram representing the disposition of eighty-four cases of lesions of the lower extremities during the year 1929.

*In these three cases, reamputation was done; they are therefore counted again under "thigh amputations" (2) and "Gritti-Stokes amputations" (1).

primarily either to infection or to arterial insufficiency with or without infection. In the former instance, the blood supply may be abnormal, even to the absence of pulsation in the peripheral vessels, but in such cases the collateral circulation has been developed to such a point that the foot is warm and essentially normal in appearance.

1. Coller, F. A., and Marsh, P. L.: Lesions of the Extremities Associated with Diabetes Mellitus, J. A. M. A. **85**:168 (July 18) 1925.

METHODS OF EXAMINATION

Almost without exception, decisions are based on clinical observations. We know of no suitable laboratory tests for the determination of the viability of a given foot under the existing conditions. In preparation for the examination, the legs of the patient from midthigh down are exposed to room temperature for at least five minutes. The most important points in estimating the circulatory background of a foot are:

Pain.—A history of pain on walking referred either to the calf of the leg or to the plantar surface of the foot suggests failing circulation. If after several months of such pain the patient becomes comfortable, he may be considered to have developed a good collateral circulation. Severe pain at rest that is out of proportion to the infection present indicates a well developed arterial insufficiency and is a bad prognostic symptom.

Appearance.—The more normal the appearance of the foot, the better is the circulation. The foot is examined in the horizontal, elevated and dependent positions. In a foot with failing circulation, the skin is frequently smooth, thin and parchment-like, and the normal contour of foot and toes is gone. Such a foot on elevation quickly assumes a cadaveric pallor which disappears very slowly when the foot is horizontal; when the foot is dependent, it becomes dusky or red and shiny, with tense, distended superficial veins.

Temperature.—Temperature changes are elicited by palpation with either the back or the palm of the hand. Beginning above the knee, a comparison is made between different levels of the same leg and similar levels of both legs. A foot that under room conditions is cold to the touch has a bad circulatory background. A sudden change of temperature at some point in the leg denotes, as a rule, absence of much collateral arterial development. In general, changes in temperature conform with changes in color and are most marked with the foot dependent.

Palpation of Peripheral Vessels.—The most important single blood vessel is the dorsalis pedis artery. Normally, pulsation can usually be felt. Buerger [2] found it in all but one of two hundred apparently normal feet. We consider the presence of good pulsation in this artery to be one of the most important observations. Any local operative procedure undertaken in its absence must be done only after careful consideration.

CONDITIONS DUE PRIMARILY TO INFECTION

In the group of conditions due primarily to infection fall our most important cases. Here, carefully selected and properly done operations, followed by painstaking after-care, have frequently resulted in saving

2. Buerger: Circulatory Diseases of the Extremities, Philadelphia, W. B. Saunders Company, 1924, p. 132.

useful feet. Proper prophylaxis would have prevented operation. One or more of the following observations are common to this group: 1. Pulsation of the dorsalis pedis artery is usually present. 2. The foot is warm and of good color. It may be definitely cooler to touch than the knee, but there is no definite level at which the change is obvious. 3. Osteomyelitis without gangrene is common. 4. Pain is only in proportion to infection and usually less than that from a similar lesion on the foot of a patient without diabetes. Not infrequently there is little or no pain, and the affected part is almost anesthetic. 5. Gangrene is found only in the presence of severe infection or after trauma.

Local operations in this group are frequently successful and usually safe.

CONDITIONS DUE PRIMARILY TO ARTERIAL INSUFFICIENCY

Extremities in which there is an insufficiency of arterial circulation are characterized by the following observations: 1. No pulsation is present in the peripheral blood vessels, including at times the femoral at the groin. 2. The foot is cold, blanches on elevation and becomes dusky or red and shiny when dependent. Between the midfoot and the knee, there is frequently a definite level at which the temperature changes. 3. Osteomyelitis with gangrene is common. 4. Pain is nearly always out of proportion to the local lesion. 5. Gangrene is common.

Local operations in this group are rarely successful and frequently are dangerous. Infection plus a painful, pulseless foot is the beginning of most cases of septicemia.

NATURE OF INFECTION

It is impossible by clinical appearances to determine the character of the organism at fault. Some of the feet, the type so frequently referred to as showing "bad streptococcus infections," have proved in cultures to be infected with *Staphylococcus aureus* or *albus*. For the diabetic patient, the most important single organism is probably *Staphylococcus albus*. Not only may it be the cause of a fatal septicemia, but its universal presence in the skin makes it the most common organism locally. It is likely that the lowered resistance of the diabetic patient permits an organism ordinarily considered more or less nonpathogenic to become of clinical importance. We have seen two cases recently in which it was recovered from the local lesion and repeatedly in pure culture from the blood stream. One of these (fatal) was seen at another hospital. The patient had a virulent infection, with gangrene, in spite of good arterial pulsation. In our patient, the organisms were also obtained in pure culture from a section of an artery and a vein removed from the leg at the time of a guillotine amputation. This patient confirmed the state-

ment of Warren [3] that this organism is ordinarily easily killed in the blood stream. He did well after a guillotine amputation through the upper third of the lower leg followed two weeks later by a Gritti-Stokes amputation (fig. 2).

Anaerobic organisms of the *Bacillus welchii* group are undoubtedly often present in gangrenous tissues. Tanner [4] reported nine cases of

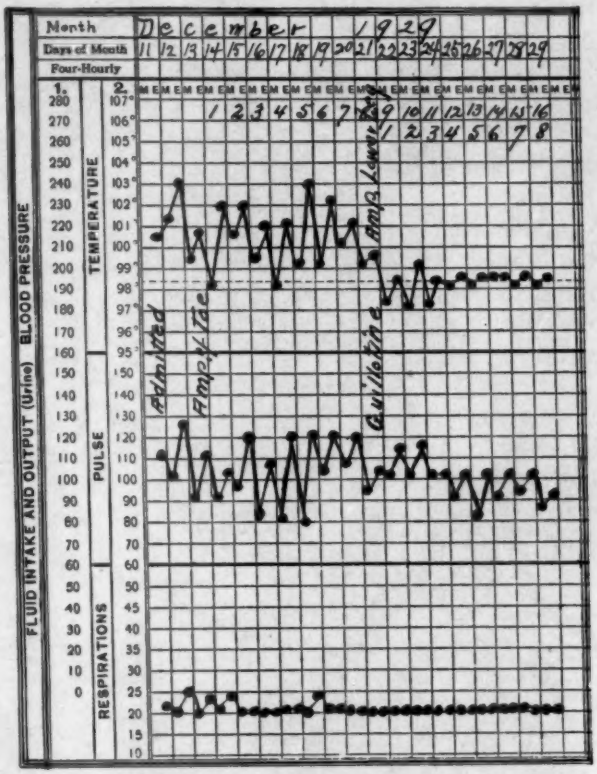

Fig. 2 (case 51931).—Chart showing progress of a man, aged 52, who had extensive infection of the left great toe with destruction of both phalanges and extension to the sole of the foot. A culture from the wound resulting from the amputation of the toe, Dec. 13, 1929, showed Staphylococcus albus. Blood cultures, Dec. 12 and Dec. 19, 1929, showed Staphylococcus albus. A section of artery and vein obtained under sterile conditions at the level of the guillotine amputation through the lower leg, Dec. 21, 1929, showed Staphylococcus albus. The failure of amputation of the toe and drainage of the foot to influence the temperature suggests the presence of organisms in the blood stream. Note the sudden and permanent drop of temperature to normal following the guillotine amputation. Gritti-Stokes amputation was done Jan. 7, 1930, and the patient was discharged, walking on an artificial leg, Jan. 28, 1930.

3. Warren, Shields: Personal communication to the authors.
4. Tanner, E. K.: S. Clin. North America **7**:1099, 1927.

gas bacillus infection in gangrenous feet. Linton [5] described six cases appearing in stumps following amputations for gangrene at the Massachusetts General Hospital. Greene [6] recently reported a similar complication. In our cases, we had one such complication, although the organisms were discovered several times in amputated specimens. The manner in which these infections develop is uncertain. Tanner was of the belief that infection of an amputation stump occurs from the presence of organisms in the blood vessels. Linton found organisms (*B. welchii*) in one of the thrombosed vessels in an amputated leg, although the possibility that these were outside rather than inside the vessels was not excluded. Greene was unable to recover any organisms of this group from the amputated leg, although they were readily recovered from the patient before death. It has been our policy to assume that such infections are contaminations from the skin introduced at the time of operation, unless there was a demonstrable gas bacillus infection before operation. For this reason, we prefer no preoperative scrub with soap and water to one carelessly done and carried too close to the gangrenous area. (See "Preparation of Patient" in later paragraphs.)

The production of gas by the ordinary pyogenic organisms is a disturbing complication. It is not uncommon to have gas escape on pressure around an open lesion. Actual crepitus is rare, although in case 51185 it was present in the stump of an amputation through the lower part of the thigh, an extensive infection of the fascia lata having developed, extending from the end of the stump to the groin (fig. 3). There was gas to the groin and the fascia was necrotic, but the muscles were normal in appearance throughout. Repeated attempts at cultivation, including that of the muscle tissue, showed only *Staphylococcus albus*. Autopsy showed multiple sepsis, but no evidence of *B. welchii*.

PRINCIPLES OF TREATMENT

The operative possibilities of a given leg can be determined by examination of the extremity. The procedure indicated for a given patient can be determined only by a careful estimate of the patient as a whole. What a waste of effort to do a lower leg or Gritti-Stokes amputation on one who, because of cerebral hemorrhage or failing eyesight, will be unable to use an artificial appliance!

Septicemia must be considered a possibility in every patient with diabetes and an infected foot. The poorer the circulation, the more difficult it is to localize infections. Repeated chills and a temperature out of proportion to the local sepsis, especially in a gangrenous foot without

5. Linton, R. R.: Latent Gas Bacillus Infection Complicating Gangrene of Lower Extremity, J. A. M. A. **95**:183 (July 19) 1930.

6. Greene, P. F.: Personal communication to the authors.

a local abscess but with lymphangitis, usually mean septicemia. A normal temperature at admission must not be construed as evidence against such a diagnosis, for within a few hours it may reach 102 or 103 F.

TREATMENT FOR INFECTIONS

Surgical solution of chlorinated soda (Dakin's solution) has proved the most satisfactory local medication in cases with infection or slough. The wounds are kept constantly wet. Normal skin is carefully pro-

Fig. 3 (case 51185).—Roentgenogram of stump from which only Staphylococcus albus could be grown, showing gas to the upper third of the thigh. There was crepitus to the groin. The muscle was normal in appearance. All of the fascia lata was necrotic. No evidence of Bacillus welchii was found at autopsy.

tected. Once the gross infection is cleaned up, a change in the type of dressing is frequently indicated; tincture of myrrh (in water 1:24), dichloramine T (from 2 to 4 per cent) in chlorinated paraffin oil and balsam of Peru have all proved helpful. The improvement of the skin following daily applications of ultraviolet rays locally seems to indicate the usefulness of these rays in the treatment for local superficial infec-

tions. Hexylresorcinol solution S T 37 (Sharpe & Dohme, in water 1:3) is nonirritating to normal skin, and has been used to advantage in such lesions as osteomyelitis of a phalanx of a toe which was being prepared for operation. We have found it of no value in the separation of a slough.

STIMULATION OF CIRCULATION

We have discontinued the use of external heat in all forms save the electric pad. The electric baker, hot water bags and hot and cold baths, when their application is left to the discretion of diabetic patients, are dangerous and ought not to be used. The feet of a diabetic patient may blister without discomfort to the patient. One of our most intelligent patients, who had taken alternating hot and cold baths for years, recently so burned one of his pulseless feet that he narrowly escaped amputation. We have seen innumerable toes taking months to heal after having been blistered by hot water bags.

The hyperemic exercises of Buerger have proved of most value. We are not prepared to explain the beneficial results to be derived from these exercises. Relief of pain in cases responding favorably is usually too early to be explained entirely on the basis of new collateral blood vessels. One gets more the impression of a readjustment of circulation to meet less drastic demands, much like the response of the heart with anginal pain to a proper relation between rest and suitable exercise. Suffice it to say that we have seen patients unable to sleep because of pain in a foot or toe who with no treatment, except rest in bed, local applications to the open lesion (if present) and Buerger exercises, become perfectly comfortable within two weeks' time and keep free from pain when up and around through carefully graded active exercise, in addition to the continuation of the passive exercises to be described later. One needs the conviction of its merits to be able to impress the average patient with the value of a procedure that seems so simple. Our routine is: (1) lying in bed with the feet elevated about 60 degrees for two minutes; (2) sitting up with the feet dependent for three minutes, and (3) assuming a horizontal position with an electric pad applied to the foot and lower part of the leg for five minutes; a total of ten minutes to the cycle, which is repeated, if the condition of the patient permits, six times each period. Hospital patients have three and in some cases four periods a day. When the pain is severe, the cycle has to be modified to suit the individual patient. Orthopedic exercises of the type ordinarily used to strengthen the muscles of the foot and limber up the toes are done when the feet are in the dependent position.

Once free from pain, the patient must be careful when again becoming active. It is our policy to start the patient walking one-half minute

out of each hour; this period is increased by one-half daily as conditions permit, and the feet are kept elevated between walks.

INDICATIONS FOR OPERATION

Gangrene.—Gangrene in a pulseless, painful foot is an indication for amputation, unless it is superficial and limited to the tip of a digit and shows evidence of healing without pain at the end of two weeks' hospital treatment consisting of rest in bed (with opiates for the first week if necessary), Buerger exercises and treatment of the local lesion.

Pain Without Actual Gangrene.—The painful, pulseless foot that after two weeks of hospital treatment is unrelieved has insufficient blood supply to be of use, and should be treated by amputation.

Osteomyelitis of a Phalanx.—Osteomyelitis of a phalanx is an indication for operation. Any unhealed ulcer of two weeks' duration overlying or on one side of an interphalangeal joint is regarded as actual or potential osteomyelitis. A positive diagnosis can be made earlier by demonstrating bare bone with a small probe than by the use of x-rays.

Recurring Ulcer.—The patient who has a recurring ulcer in a callus on a toe which, with proper care of the feet, cannot be kept healed is more safely treated by amputation of the toe than by conservative treatment.

Extensive Infection.—Extensive infection is an indication for operation.

SELECTION OF THE TYPE OF OPERATION

The visualization of the arterial background of the limb is essential to the proper handling of a patient with a circulatory condition. If all peripheral vessels pulsate, this is not difficult. The extent of the local lesion, however, is of little help. There may be complete gangrene of a toe, yet a good result may be obtained by proper local amputation, whereas a toe without gangrene but with a painful ulcer may require an amputation through the thigh for relief. Figure 4 represents (*A* and *B*) legs amputated for gangrene. Figure 4 *A* shows characteristic irregular narrowing of arteriosclerotic blood vessels with complete occlusion of all three vessels to the foot. It is therefore obvious that in this type of leg, any operative procedure, to be successful, must be done through a point well supplied by the main vessels. Figure 4 *B*, on the other hand, shows no filling of consequence in the main blood vessels, but shows an extraordinary development of collateral vessels. This type of leg, which is warm and of fairly good color, without a definite line of temperature change, offers possibilities of local operative procedures below the level of any main blood vessel. In fact, highly developed circulation of this type is a better background for a Gritti-Stokes amputation than a good popliteal artery with few collaterals.

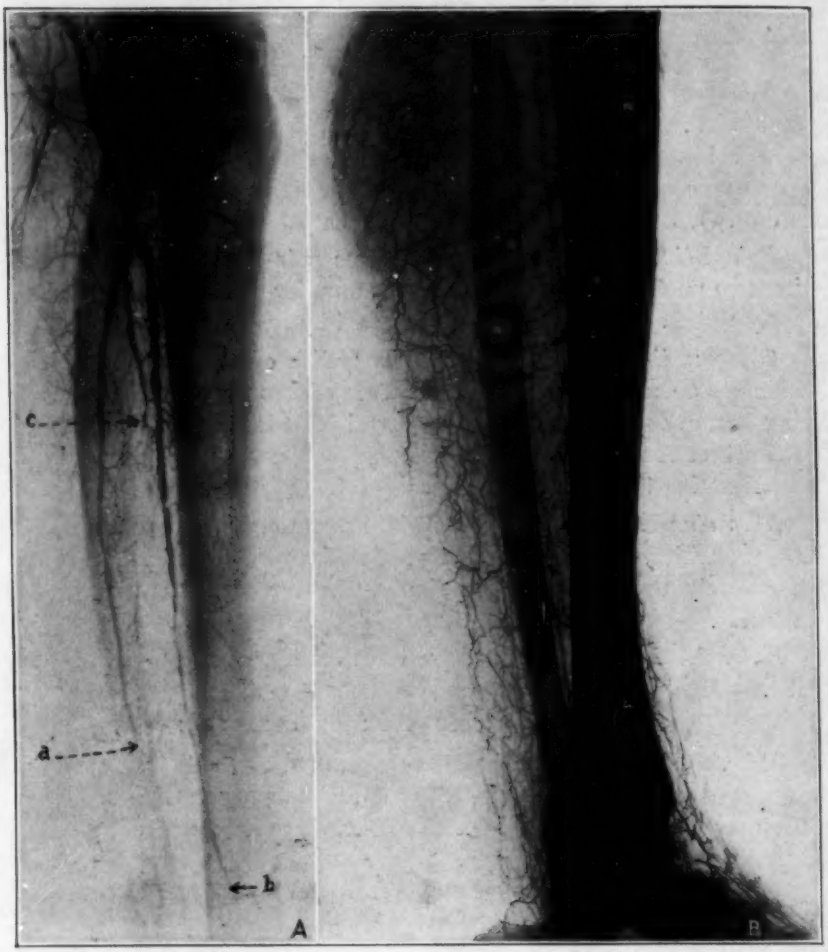

Fig. 4 (case 28863).—*A*, low thigh amputation in a patient, aged 72, for gangrene of the first, second and fourth toes. Injection of the femoral artery with a fine suspension of barium sulphate. Note the irregularity of the lumen of each main vessel, the abrupt ending of the injection at *a*, *b* and *c* due to an occluding thrombus. Note also to what a slight degree the collateral circulation has been developed. (The illustration is from McKittrick and Root; Diabetic Surgery, Philadelphia, Lea & Febiger, 1928.)

B (case 42419), unsuccessful amputation of the fifth toe for gangrene followed by Gritti-Stokes amputation with a good result in a man, aged 67. Injection of the amputated limb with a fine suspension of barium sulphate showing extensive development of collateral circulation.

INDICATIONS FOR THE AMPUTATION OF ONE OR MORE TOES

Any local amputation in the absence of pulsation in the dorsalis pedis artery must be undertaken only after careful consideration. The high mortality of patients with reamputations [7] comes from ill advised amputations of toes in feet with insufficient circulation to prevent infection of the blood stream. In general, amputation of one or more toes may be tried for: (1) Gangrene of a toe or portion of a toe, with good pulsation in the dorsalis pedis artery and a warm foot. Occasionally, in the absence of such pulsation, a patient having a toe with a gangrenous tip resulting from trauma will do well after amputation of the toe, if the foot is warm, of good color and with no definite level of temperature change. (2) Osteomyelitis of a phalanx without gangrene. (3) Chronic ulcera-

Fig. 5 (case 30128).—Gangrenous slough on the dorsum of the foot with extension of the infection between the third and fourth metatarsals in a woman, aged 76. Dorsal incision was used. (McKittrick and Root: Diabetic Surgery, Philadelphia, Lea & Febiger, 1928.)

tion in a corn or callus that fails to remain healed under conservative treatment. (4) More complete drainage in cases of infection between toes or involving deeper structures of the foot (figs. 5, 6 and 7).

AMPUTATION THROUGH THE LOWER LEG

The great advantage of an amputation through the lower leg is that gained from preservation of the use of the knee joint. Amputation through the lower leg can be done more frequently than is desirable

7. Eliason and Wright: Surg. Gynec. Obst. **42**:753, 1926.

because of the susceptibility of such a stump to pressure sores. It is a rational surgical procedure if the patient is in good general condition without a rapidly spreading infection and if (1) the skin of the leg is warm and of good color to the level of the ankle, (2) there is good pulsation in the popliteal artery and (3) there is no evidence of lymphangitis or phlebitis above the ankle.

When all of these conditions are fulfilled, it is the operation of choice in: (1) a woman under 60 years of age, unless from economic necessity

Fig. 6 (case 30128).—The same foot as that in figure 5, showing operative wound. Removal of third, fourth and fifth toes with portions of the third and fourth metatarsals was necessary for proper drainage. (McKittrick and Root: Diabetic Surgery, Philadelphia, Lea & Febiger, 1928.)

she must be on her feet most of the day; (2) a man under 55 years of age, if operation is done because of a localized infection and not for gangrene and provided he lives relatively near an artificial limb-maker and his occupation does not make it necessary for him to be on his feet for long periods of time (see indications for Gritti-Stokes amputation); and (3) a patient in whom the condition of the other foot is such that

subsequent trouble seems probable. In the latter case, it may be advisable to do an amputation through the lower part of the leg at the first operation for fear that a higher amputation may be needed eventually on the opposite side. Probably the best combination in a double amputation is an amputation through the lower part of the leg on both sides or a Gritti-Stokes amputation on one side and an amputation through the lower part of the leg on the other.

GRITTI-STOKES AMPUTATION

From the point of view of service, a Gritti-Stokes amputation gives the most efficient stump above the level of a Symes amputation. The

Fig. 7 (case 30128).—The same foot as that in figure 6, showing the end-result eight weeks after operation. Good anatomic and functional result. (McKittrick and Root: Diabetic Surgery, Philadelphia, Lea & Febiger, 1928.)

operation is a little more complicated than an amputation through the thigh, the blood supply to the flaps is not so good, and healing is a little more irregular. The surgical requirements for a Gritti-Stokes amputation are: (1) good pulsation in the popliteal artery or unusual collateral circulation, evidenced by warm skin and good color to the level of the ankle; (2) absence of lymphangitis, phlebitis or other signs of infection

to a point at least 3 inches (7.5 cm.) below the level of the tibial spine; (3) no clinical or bacteriologic evidence of a general septicemia, and (4) a patient whose general condition suggests the probability of his using some type of artificial limb.

If all of the conditions enumerated are fulfilled, this operation is indicated in: (1) a patient who has an amputation done because of deficient circulation, particularly if that patient must earn a living on his feet; (2) a patient who wishes to have a stump free from trouble at the expense of a more normal gait, and (3) an elderly patient who, because of the confidence and the comfort inspired by a long, end-bearing stump, might be able to get around on a peg leg, rather than be confined to a wheel chair.

AMPUTATION THROUGH THE THIGH

The indications for an amputation through the thigh are: (1) a condition permitting primary suture and requiring the shortest and surest operation; (2) conditions that will prevent subsequent use of an artificial limb, such as failing eyesight (not due to cataracts), mental instability, etc.; (3) inability to feel any popliteal pulsation, unless the skin is warm and of good color at least to the level of the ankle; (4) failure to palpate the femoral artery in the groin, and (5) extensive infection which makes lower amputation unwise.

GUILLOTINE AMPUTATION

By this operation, we mean the classic guillotine procedure: Skin, muscles and bone are all cut in the same plane, the operation being done quickly with minimum manipulation. Dakin's tubes are sutured over the end of the stump, and irrigations are begun at once and continued every two hours. The amputation should be done above the gross infection (not above lymphangitis) through tissue with good circulation; usually through the upper third of the lower leg. In every instance, except when amputation is above the knee, a reamputation is done within two or three weeks, if the patient does well. A patient whose response to a guillotine amputation is satisfactory has a sudden and permanent fall in temperature to or slightly above normal (fig. 2). If the response is otherwise, secondary infection is usually present, and reamputation should be done only after every possible effort has been made to find a source of infection to explain the failure to obtain the desired response. Compare figures 8 and 2.

The use of the guillotine amputation is restricted to: (1) the patient with septicemia, actual or suspected, from a badly infected or gangrenous foot; (2) the very sick patient with extensive sepsis, and (3) the patient who has a gangrenous foot with extensive lymphangitis, in whose case primary suture would be unsafe.

ANESTHESIA

Spinal anesthesia obtained with procaine hydrochloride [8] has been the anesthesia of choice, although that obtained with ethylene and oxygen or with nitrous oxide and oxygen has proved satisfactory for the shorter operations. Ether or chloroform should never be given, and procaine hydrochloride locally only in carefully selected cases in which the local circulation is good and in which injection can be made proximal to any infection that may be present. Our own tendency has been to use more

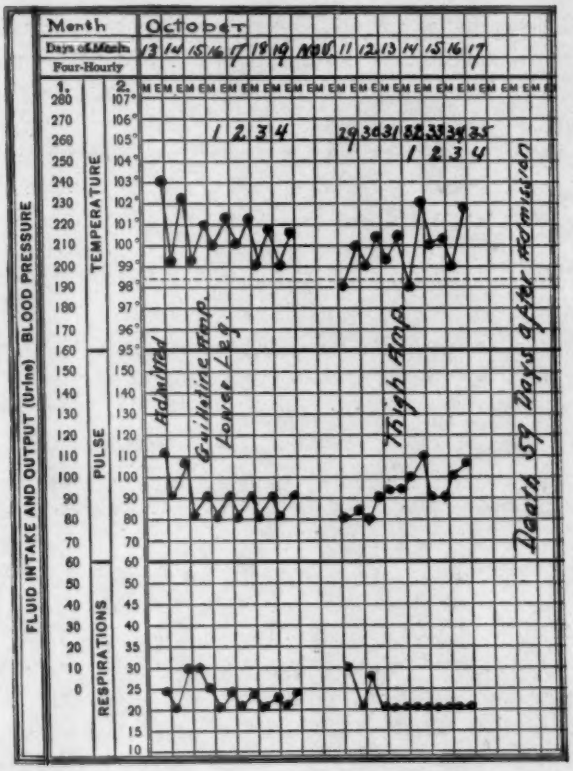

Fig. 8 (case 51185).—A chart showing the postoperative course of a man, aged 68, who had gangrene, infection and lymphangitis to the knee on admission to the hospital. Blood cultures disclosed Streptococcus hemolyticus. All subsequent blood cultures were negative. The failure of the temperature to become and remain normal after guillotine amputation is suggestive of infection elsewhere than in the stump. The failure to find this resulted in reamputation (through the thigh) thirty-one days later, with breaking down of the stump and death thirty days later. Autopsy showed a left subdiaphragmatic abscess and a small localized empyema on the left.

8. We still prefer the "C" tablets of procain (Metz), according to the technic previously described (McKittrick, L. S., and Root, H. F.: Diabetic Surgery, Philadelphia, Lea & Febiger, 1928, p. 86).

rather than less spinal anesthesia even for simple toe amputations. In this series of cases, no patient had a reaction of sufficient severity to warrant any type of stimulation. Except for an occasional case, the level of anesthesia does not go above the crest of the ileum, and for operations in the foot, rarely above the knee. Safety and satisfaction, however, come not so much from the type of solution used as from the experience of the one who gives it. We prefer not to use any preoperative opiate.

TECHNICAL POINTS

In diabetic patients, operative procedures, to be successful, must be based on certain fundamental principles: 1. Circulation must be adequate to localize infection and permit repair to take place. 2. Drainage must be dependent and complete. A continuous incision is preferable to counter incisions (fig. 9). 3. Incisions must be so placed as to minimize interference with the blood supply and, at the same time, permit extension of the wound should further infection occur.

AMPUTATION OF ONE OR MORE TOES WITHOUT DRAINAGE OF THE FOOT

The most common lesion requiring local operation on a foot with good circulation is osteomyelitis of a phalanx involving either a joint or the distal phalanx. A lesion of this type is usually of long standing with an established chronic sinus. The acute exacerbations nearly always quiet down on rest in bed and the application of surgical solution of chlorinated soda (Dakin's solution) locally. There is undoubtedly considerable local immunity, so that the wound, if amputation is done proximal to the lesion and if the sinus is not opened, can usually be sutured loosely with a fine skin suture, healing resulting in from a week to ten days. Experience has shown that it is better not to close the wound if there is no pulsation in the dorsalis pedis artery or if the sinus has been opened.

Any amputation of a toe for gangrene, regardless of the presence of a patent dorsalis pedis artery, is safer if the wound is loosely packed with dry gauze than if it is sutured.

AMPUTATION OF ONE OR MORE TOES WITH DRAINAGE OF THE FOOT

Proper drainage of a foot in which infection has extended into the deeper structures represents the most important phase of a surgical procedure on a diabetic patient. This is of particular note because it occurs in a patient with good circulation; otherwise, gangrene and possibly septicemia would have developed. It is also of importance because, if it is not properly done, the process is sure to extend, the diabetic situation becomes worse and, finally, either the loss of a limb or death results.

Grodinsky,[9] by painstaking work on fascial spaces of the foot, made a valuable contribution to surgery of the lower extremities. Not having had the benefit of such a definite anatomic study in the past, we are unable to say how closely the spread of infection has followed the lines he described. We are pleased, however, to give support to his suggestion that drainage of these deep infections should be done through an incision other than one on the plantar surface of the foot. The latter is

Fig. 9 (case 52340).—Extensive infection arising from an ulcer on the lateral aspect of the foot with extension to and destruction of the fifth metatarsophalangeal joint in a man, aged 61. There was also a subcutaneous extension running along under the base of the toes to the medial aspect of the head of the first metatarsal. Note that one continuous incision was used to drain the entire infected area. The fourth toe was not involved, but its removal was necessary in order to insure adequate drainage. There are no counter incisions. A good result was obtained without subsequent operation. See figure 10*A*.

all that he said of it: unsatifactory from the point of drainage, bad from the point of scarring and, in addition, conducive to infection of the sub-

9. Grodinsky, M.: Surg. Gynec. Obst. **49**:737, 1929.

cutaneous tissues of the foot, the resistance of which is extremely low. On a sound anatomic basis, he recommended the use of a medial incision.

With but few exceptions, we use a racquet type of incision for the amputation of a toe. Ordinarily the arm of the racquet is on the dorsum of the foot. Since October, 1925, we have so placed the incision for amputation of the first toe that whenever there is a possibility that the infection has extended or may extend to the deeper structures of the foot, the arm of the racquet is on the medial side of the foot. This part of the incision may then be continued either at the first or at subsequent operations to the inner aspect of the heel, if necessary. Except for the occasional case in which there is unusually good local circulation and in which the infection is still localized within the joint, the head, including, if necessary, a portion of the shaft of the metatarsal, is removed. This is beveled in such a way that the base of the wound is smooth, with its lowest point nearest the heel. If the infection has extended toward the lateral side of the foot, it is usually advisable to remove the second toe, including a portion of its metatarsal, in order that the cavity may be sufficiently open to give the complete drainage that is essential. Dakin's tubes are placed at operation, and two-hourly irrigations with surgical solution of chlorinated soda (Dakin's solution) are instituted when the patient reaches the ward. In this way, the submetatarsal area may be satisfactorily drained. In general, the sesamoid bones are removed; always, in case the infection is from a perforating ulcer situated under the head of the first metatarsal.

In cases in which the fifth rather than the first toe is involved, a similar procedure is carried out (figs. 9 and 10 *A*). When the incision is along the medial or lateral aspect of the foot, it is well to make it more toward the dorsal than toward the plantar surface.

Infection originating from the middle toes is more difficult to drain. In this case we prefer a dorsal incision, removing as many toes as necessary and from the point at which infection is greatest extending the incision as far on the dorsum of the foot as is necessary. Here, too, free removal of the metatarsals is essential to complete drainage, and to make the final wound such that it will drain freely toward its most dependent point (fig. 10 *B*).

The drastic removal of bone support in these operations was first undertaken on the basis that a useful though imperfect foot was better than none. Much to our surprise, the functional result has been entirely satisfactory, so that we no longer have any hesitancy about removing as much bone as is necessary.

Secondary operations are not infrequent. There may be some extension requiring additional incisions or the removal of more bone. Great care is taken not to break up recently formed adhesions in an effort to hasten separation of sloughing tendons or fascia. Where

clean tendons are cut across, the tendon is left longer than its sheath, and a small piece of dry gauze is packed against it in the hope of hastening adhesions to prevent the spread of infection. In all such operative procedures, Dakin's tubes are used, and irrigations every two hours are begun as soon as the patient returns to the ward.

Following operative trauma, there is usually a slight elevation of temperature which should reach normal within a few days and remain so if progress is satisfactory. Any real tenderness in the sole of the foot means extension of infection and will, as a rule, require further operation. Any suggestion of an infection of the blood stream,

Fig. 10 *A* (case 52340).—The same foot as that in figure 9, showing the manner in which the fifth and fourth metatarsals were removed in order to give satisfactory drainage to an infection that had extended from the fifth toe. Note that the fifth metatarsal was made shorter than the fourth and was beveled in order that all parts of the wound should slant to the lowest point.

B (case 36546).—Foot of a patient, aged 51, showing the extent to which the metatarsals were removed in giving drainage to a deep infection from the middle toes. In this case, infection had extended from an infected callus on the ball of the foot through to the dorsum of the foot. The dorsalis pedis was not felt (edema), but circulation was good. A dorsal incision was used. There was involvement of the flexor tendon of the third toe with pus underneath and between the third and fourth metatarsals. Complete healing occurred in two months.

such as chills, lymphangitis and a fever out of proportion to the local sepsis, must be met at once with a guillotine amputation through the

upper third of the lower leg. If cases are properly selected, however, and operation carefully done, this complication ought to occur rarely.

MAJOR AMPUTATIONS

The complete details of major amputations have already been described.[10] A brief résumé of the most important points must therefore suffice at this time.

Preparation of the Skin.—We are more and more impressed with skin contamination as a cause of postoperative infection of amputation stumps, if *Staphylococcus albus* is to be considered a fair criterion of the source of infection. Preoperative preparation and operative technic are of greatest importance. Whenever possible, the field of operation is prepared by at least one careful scrubbing with tincture of green soap, followed by alcohol and ether and an application of 5 per cent acriflavine in 50 per cent alcohol and acetone.[11] Great care is taken never to scrub or to manipulate the skin more than 2 inches (5 cm.) below the line of incision in the fear, particularly, that such manipulation may stir up an infection in the lymphatics and that gas bacilli may be wiped from the skin in the neighborhood of the gangrenous area into the operative field.

Tourniquets.—Tourniquets are never used except in guillotine amputations. We fear fresh thrombosis following a trauma sufficient to occlude temporarily the sclerotic blood vessels.

Flaps.—Equal lateral flaps are used in amputations through the lower part of the leg. A long anterior flap is necessary in a Gritti-Stokes amputation. All amputations through the thigh are done with a circular incision. This minimizes interference with circulation, and the resulting stumps are good. Care is taken to have the fascia come together over the end of the bone snugly, but without undue tension. Hemostasis must be complete, but not at the expense of too much manipulation. Precision and a minimum of manipulation are essential. No instrument, sponge or finger allowed to touch the skin is used inside the wound.

Nerves.—Absolute alcohol is injected into the nerves, as recommended by Lewis and Huber.[12]

Drainage.—We have followed the teachings of Jones[13] and have closed all of our amputation stumps without drainage, except when a guillotine amputation was done. We believe that this procedure short-

10. McKittrick and Root (footnote 8, p. 168).

11. Tinker, M. B., and Sutton, H. B.: Skin Disinfection with Especial Reference to Use of Acriflavine, J. A. M. A. **98**:1560 (May 14) 1927.

12. Huber, G. C., and Lewis, Dean: Amputation Neuromas: Their Development and Prevention, Arch. Surg. **1**:85 (July) 1920.

13. Jones, D. F.: Personal communication to the authors.

ens convalescence and lessens the possibility of sepsis in the stump and an adherent scar. In each of two series of amputations reported, in which both methods were compared, the results were in favor of stumps not drained.[14]

POSTOPERATIVE CARE

It would seem that all possible misfortunes had come to us in the care of this group of patients; infections of the back, varying from small superficial pustules to fatal carbuncles, ordinary sacral pressure sores and, what was probably the most time-consuming, pressure areas on the remaining heel following amputation, requiring weeks of additional hospital care. In an effort to minimize such complications, the following routine has been adopted: 1. A balkan frame is attached to each bed as a part of the preparation for amputation. This facilitates movements in bed and lessens the tendency of the patient to push himself up in bed by digging his heel into the mattress. 2. A heavy woolen sock is provided, which affords some protection from pressure; it is removed daily and the foot massaged with hydrous wool fat. 3. A hair pillow, 26 inches by 13 inches by 4 inches, is placed under the leg (or legs) just above the heel to prevent contact between it and the mattress. 4. Ultraviolet rays are applied daily to the back of any patient whose skin shows the slightest evidence of irritation.

In a normal convalescence from an amputation, the dressing of the stump is changed in from six to eight days. Following a Gritti-Stokes amputation, the sutures can usually be removed in ten days. Care must be taken after amputations through the lower part of the leg or the thigh, however, not to remove all the sutures until from ten to fourteen days after operation, and even then it is usually wise to relieve some of the tension by adhesive strips. Continued elevation of temperature to 100.6 F. or above, steady pain in the stump, swelling of the limb above the level of amputation or tenderness along the blood vessels are indications for earlier inspection of the dressing. Even then a stump may appear white, soft and dry at the end of three days, whereas in ten days it will be the seat of an extensive infection. If in a patient under suspicion of having septicemia the immediate drop in temperature that occurs after operation is followed by a rise to preoperative level, with but few exceptions the patient either has septicemia or an extensive local infection, probably deep, and all sutures should be removed including those of the fascia, unless sufficient sepsis is found in the subcutaneous tissues to explain the temperature and unless removal of skin sutures results in a fall in temperature. Such a wound should be irrigated with Dakin's solution every two hours just as after a guillotine amputation.

14. Eliason and Wright (footnote 7). Kuhns, J., and Wilson, P. D.: Major Amputations: Analysis and Study of End-High Results in 420 Cases, Arch. Surg. **16**:887 (April) 1928.

Artificial Limbs.—It is our aim to have all patients who have had a Gritti-Stokes amputation and those who have had a routine amputation through the thigh, whom we expect to use artificial legs, walk without direct assistance before leaving the hospital. These patients are measured for temporary peg legs (fig. 11). As soon as their stumps and general condition are satisfactory (from ten to twelve days after operation), and they begin to walk with a leg and crutches near the end of the third week. It has been found that if these patients are taught to

Fig. 11.—Type of peg leg (temporary) used after a Gritti-Stokes amputation or an amputation through the thigh. In the former case, one or more felt pads placed in the bottom of the bucket are used to obtain end-bearing. (This peg leg was made by the Boston Artificial Limb Company.)

walk before going home, they will continue to do so; if not, many of the older people content themselves with the wheel chair and crutches. It takes the incentive of going home to stimulate them to a conscientious attempt to learn. Those for whom it seems worth while are fitted with permanent legs when the condition of the stump permits (fig. 12). As a rule, patients with an amputation are not fitted with temporary legs below the knee until four or five weeks after operation.

RESULTS OF OPERATIONS

Table 1 represents a summary of operations done by one of us between May, 1923, and Jan. 1, 1930. Such a mortality table cannot be interpreted without an understanding of conditions at the time of operation. Suffice it to say that only those patients whose life expectancy seemed to be days rather than weeks were not offered operation (three in the series). All other patients were offered the comfort that amputation of an infected and usually gangrenous leg offered. With but two or

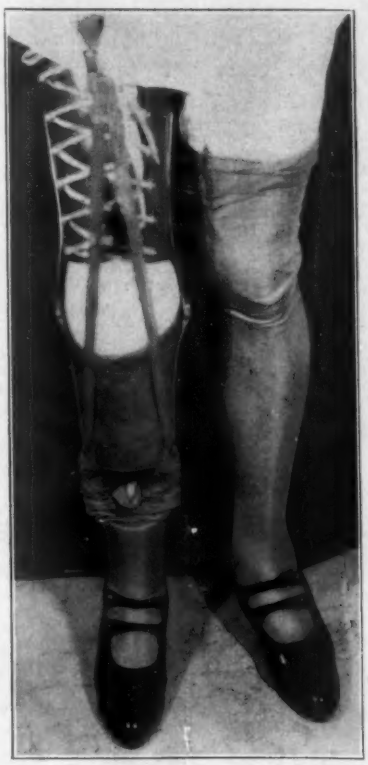

Fig. 12.—Temporary artificial leg used following an amputation through the upper third of the lower part of the leg. It is modified from the leg described by Wilson (J. Bone & Joint Surg. **4**:224, 1922). The bucket is made of leather, and laces in the back in order to take care of shrinkage of the stump. The end is open.

three exceptions, it was accepted. The mortality is high, especially in conditions in which arterial insufficiency is the primary factor. The danger of ill advised delay in this group must be constantly kept in mind in any plan of treatment, and every precaution taken to avoid conservative operations in cases in which there is insufficient circulation to warrant it. An effort to save a leg in case 50625, that of a man, 72 years of age, with a small gangrenous area around the nail, cost him sixteen

weeks in the hospital and his life from sepsis. It was realized that he had too little circulation to warrant amputation of the toe, but it was felt that it might be possible for the necrotic tip to separate and heal itself. The distal interphalangeal joint became involved; the removal of the tip of the middle phalanx was followed by extension of infection along the tendon, a Gritti-Stokes amputation, sepsis and death. A Gritti-Stokes operation on this patient when he was first seen would undoubtedly have been successful. This so-called conservative treatment of gangrene has proved unsuccessful in our hands, and we suspect that many patients who do well with this type of treatment would save time with a local amputation properly done. Surely, the patients whom we have seen with actual gangrenous destruction of the tip of a toe that we have not dared to amputate have not responded well to conservative treatment. This

TABLE 1.—*Operations from 1923 to 1929, Inclusive*

Amputation	Number of Cases			Number of Operations	Deaths		
	Gangrene	Infection	Total		Gangrene	Infection	Total
One or more toes	14	71	85	90	2 (14.3%)	0	2 (2.3%)
Toe, then major	23	7	30	65	3 (13%)	2 (28.5%)	5 (16.6%)
Through lower leg	10	4	14	15*	0	0	0
Through lower leg, then through thigh	1	0	1	2	0	0	0
Guillotine through lower leg	2	0	2	2	2 (100%)	0	2 (100%)
Guillotine through lower leg, then amputation through thigh	4	0	4	8	2	0	2 (50%)
Guillotine through lower leg, then Gritti-Stokes	3	1	4	8	0	0	0
Gritti-Stokes	33	2	35	35	5 (15.1%)	0	5 (14.3%)
Gritti-Stokes then through thigh	1	0	1	2	1	0	1 (100%)
Through thigh	41	5	46	46	7 (17%)	0	7 (15.2%)
Death under anesthesia, no operation	1	0	1	..	1	0	1
Total of amputations	133	90	223	273	23 (17.2%)	2 (2.2%)	25 (11.2%)
Incision and drainage	0	8	8	8	0	2 (25%)	2 (25%)
Total of operations	133	98	231	281	23 (17.2%)	4 (4.1%)	27 (11.6%)
Summary of Amputations							
Amputation of one or more toes	14	71	85	90	2 (14.3%)	0	2 (2.3%)
Amputation of one or more toes, including that followed by major operation	37	78	115	155	5 (13.5%)	2 (2.56%)	7 (6.08%)
Major amputation	119	19	138	..	21 (17.6%)	2 (10.5%)	23 (16.6%)

* Ligation of popliteal vein preceded amputation.

does not include patients who have a small area of superficial gangrenous slough near the tip of a toe, in whom the response to treatment is definite within two weeks.

The relatively few patients who have had an operation on the lower extremity that did not include the removal of one or more toes is noteworthy. This is readily understood when one appreciates the fact that most infections of feet needing operation arise from infection of a toe, and that it is only rarely possible to drain adequately a deep infection in a diabetic patient without the additional advantage afforded by the sacrifice of one or more toes.

The patients who have survived a guillotine operation represent lives saved that undoubtedly would have been lost had a primary closure been attempted.

From figure 1 it will be seen that more than half (forty-three of eighty-four) of the patients seen during the past year were treated without operation. Almost half of those operated on (seventeen of forty-one) had a successful amputation of one or more toes. Amputation through the lower part of the leg, in 1923 the most frequent operation, has given way to the Gritti-Stokes amputation, not because immediate results are better, but because the resulting stump is more practical. It will also be noted that the increase in number of conservative amputations has been accomplished without increasing the mortality.

TABLE 2.—*Operations for Bilateral Gangrene from 1923 to 1929, Inclusive*

Case	Sex of Patient	Age of Patient		Interval
		At First Operation, Year	At Second Operation, Year	
3210	F	64	65*	1 yr., 3 mo.
3745	M	58	63	5 yr.
3834	F	70	71	8 mo.
3806	M	53	64	11 yr.
24133	M	59	60	1 yr.
3519	M	63	64	1 yr.
3724	F	63	63*	2 mo.
5250	M	59	59	3 mo.
30675	F	51	51*	3 days
3280	F	64	67	3 yr.
4108	M	68	75	7 yr.
4721	F	59	60†	1½ yr.
4290	F	65	67*	1½ yr.
23020	M	70	71	1 yr., 4 mo.
42489	F	63	65†	2 yr.
43870	M	65	65	3 wk.
36970	F	68	70	2 yr.
39120	F	59	67†	8 yr.
51636	M	68	79†	11 yr.
28863	M	72	74*	2 yr.
22383	M	68	69*	1 yr.
40018	F	69	70*	1 yr.

* Not operated on.
† One operation elsewhere.

Reamputations.—There has been an increase in the number of reamputations. Prior to Jan. 1, 1927, amputation of one or more toes was followed by a higher operation in six cases, with a mortality of 16.6 per cent. During this period there was no instance of gangrene or infection in the stump from a major amputation requiring reamputation. Between Jan. 1, 1927, and Jan. 1, 1930, there were twenty-four unsuccessful toe amputations. The mortality has remained the same. This increase in the number of operations without a corresponding increase in the mortality occurred in that group of patients in whom only clinical trial would definitely determine the outcome. Greater experience enlarged the number of patients on whom such a procedure was deemed safe. During this latter period there was one amputation through the upper third of the lower part of the leg following which infection necessitated a guil-

lotine amputation above the knee, and one ill chosen Gritti-Stokes amputation which at the first sign of infection of the stump was followed by a reamputation through the midthigh because of the poor general condition. This stump was solidly healed in twelve days, although the patient finally died of urinary sepsis and renal insufficiency. Eight patients with guillotine amputations survived the initial infection so that reamputation was deemed advisable. Two of these died, one of late metastatic sepsis though his thigh stump was solidly healed; the other, the patient in case 51185, has been mentioned.

TABLE 3.—*Causes of Death After Operation for Gangrene or Infection from 1923 to 1929, Inclusive*

Case	Duration of Lesion Before Operation	Amputation	Day of Death	Cause of Death
		Condition: Primary Arterial Insufficiency		
30875	?	Thigh	4	Preoperative streptococcus septicemia; auricular fibrillation; embolic gangrene in other leg
3798	8 wk.	Gritti-Stokes	10	Preoperative Streptococcus hemolyticus septicemia (autopsy)
3036	6 wk.	Thigh	4	Preoperative clinical septicemia; not proved
4820	1 mo.	Thigh	53	Stump healed; terminal bronchopneumonia (autopsy)
3971	5 wk.	Gritti-Stokes	4	Preoperative streptococcus septicemia
3631	?	Thigh	1	Preoperative streptococcus septicemia with acute glossitis and pharyngitis (autopsy)
5254	3 wk.	Toe	3	Pulmonary embolus (autopsy)
35140	3 mo.	Gritti-Stokes	7	Infection of stump with gas bacillus (autopsy)
3503	4 wk.	Thigh	3	Terminal bronchopneumonia
4326	3 wk.	Toe; Gritti-Stokes	35	Postoperative streptococcus septicemia following erysipelas of stump
47311	2 wk.	Gritti-Stokes	10	Preoperative streptococcus septicemia
4108	2 mo.	(No operation)	..	Died under ethylene before operation started
6464	3 wk.	Guillotine	25	Preoperative general septicemia
5948	3 wk.	Toe; Gritti-Stokes	8	Postoperative general septicemia
45504	?	Thigh	47	Postoperative Staphylococcus aureus septicemia
45852	?	Gritti-Stokes	139	Urinary sepsis plus uremia; stump healed
42589	1 wk.	Guillotine	40	Questionable pulmonary embolus (no autopsy)
41904	1 mo.	Gritti-Stokes	16	Sudden; stump healed
50625	4 wk.	Gritti-Stokes	44	Postoperative sepsis
51205	2 wk.	Thigh	8	Coronary thrombosis; sepsis of stump
51636	6 mo.	Thigh	45	Terminal bronchopneumonia
51185	3 wk.	Guillotine	57	Preoperative streptococcus septicemia
		Condition: Primarily Infection		
4507	?	Toe; thigh	6	Preoperative Staphylococcus aureus septicemia
3468	16 days	Incision and drainage	9	Postoperative streptococcus septicemia
43390	5 mo.	Toe	15	Coronary thrombosis (autopsy)
45829	?	Guillotine	23	Infection of foot with gas bacillus, plus empyema
31245	?	Toe; Gritti-Stokes	64	Sepsis of stump

Double Amputations.—Amputation of one foot is no contraindication to similar treatment for gangrene of the other. We have numbered among our most grateful patients those who, confined to bed with a painful, foul-smelling gangrene of the remaining foot, have received the comfort offered by amputation. In case 3519, the patient had an amputation through the lower part of the leg performed by Dr. D. F. Jones in September, 1923, after suffering the pain of a gangrenous foot for six weeks. One year later, he returned to the hospital two weeks after a similar accident to his good foot, requesting operation as soon as possible. A Gritti-Stokes amputation was done. The same patient at the age of 69 was able to work in his garden, and in January, 1929, he

wrote that he was "feeling better than for years." The number of cases of bilateral gangrene occurring in this series is shown in table 2.

Tables 3 and 4 represent the causes of death in these patients. It is interesting to note that infection remains the predominating factor, owing either to delay in receiving proper treatment (nine) or to infection following operation (seven). Earlier and better surgical treatment still offers much toward lowering the death rate in these patients.

TABLE 4.—*Summary of Deaths (Hospital) Following Operations for Gangrene or Infection, from 1923 to 1929, Inclusive*

Cause	Deaths
General septicemia, preoperative	9
General septicemia, postoperative	4
Sepsis, postoperative	3
Infection of stump with gas bacillus	1
Infection of foot with gas bacillus; empyema	1
Terminal bronchopneumonia	3
Pulmonary embolus	2*
Coronary thrombosis	2*
Sudden death under anesthesia	1
Cardiorenal disease	1
	27

* One autopsy.

SUMMARY

Two hundred eighty-one operations for lesions of the lower extremities in patients with diabetes mellitus form the basis of this report. These lesions are classified into (1) those due to arterial insufficiency and (2) those due primarily to infection. The importance of such a classification is demonstrated by the results obtained.

Staphylococcus albus has proved of great importance in operations on diabetic patients. It is the organism most frequently found in cases of minor sepsis of the feet and may be the cause of fatal septicemia. Gas bacillus infection following amputation for gangrene has been a rare complication in this series. Production of gas in wounds infected by staphylococci and streptococci has been frequently seen.

The passive exercises of Buerger have proved the most satisfactory method of stimulating circulation.

Indications for the various types of operation done are discussed.

The 281 operations represent 231 separate conditions with a mortality of 11.6 per cent. The mortality in 119 major amputations for conditions primarily due to arterial insufficiency was 17.6 per cent, and in 19 amputations for conditions primarily due to infection was 10.5 per cent, a combined mortality of 16.6 per cent. These patients died of the surgical conditions.

Spinal anesthesia has been the anesthesia of choice.

Early and proper treatment of the surgical lesions will do much to prevent preoperative and postoperative septicemia, the cause of death in 50 per cent of these patients.

SPINAL ANESTHESIA IN THE NEAR EAST*

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Surgical studies and investigations are made more and more in large hospitals where resources are unlimited and assistants numerous. It is evident that there spinal anesthesia has a large place. But much of the world's surgical work is done, and more will be done, far from such centers, as simpler surgical procedures, such as herniotomies and interval appendectomies, are standardized and turned over to the general practitioner.

The surgeon who works with simple equipment and few assistants finds anesthesia his major technical problem. The Mayo Clinic can report the use of general anesthesia in 50,000 cases without a death, but inexpert anesthetists, at least in the Near East, have a very different record. Moreover, the disadvantages of general anesthesia are not limited to its occasional fatalities. Every surgeon in this part of the world has given artificial respiration dozens of times because his patient had received too much anesthetic, and much more often his aseptic field has been kicked to pieces because the patient had not had enough. Deaths from postoperative hemorrhage are rare; I have not seen one. There has been one death from infection. Most of the unavoidable dangers which still threaten a patient are connected with the anesthesia.

THE PROBLEMS OF ANESTHESIA

My previous experience with spinal anesthesia was not fortunate. The convenience of the method is obvious, but it was followed sometimes by very alarming shock and more often by severe headaches, which might last for days, and by paralysis of the bladder requiring long-continued catheterization. Pitkin's articles recalled my attention to this method, and from them as a foundation, I have developed a procedure which seems satisfactory even in this primitive country, so it may be worth reporting. Spinal anesthesia is now used for practically all work below the diaphragm. The subject divided itself into six separate problems.

1. *The Spinal Puncture.*—It is not always easy to introduce the needle. Twice I was defeated in spite of all efforts. The interspinous ligament is tough, and it is difficult to keep the needle in the median plane while passing through it. On the basis of an idea that came from

* Submitted for publication, March 14, 1930.

the Lahey Clinic in Boston, the guide shown in figure 1 was made. After careful anesthetization of the skin and the structures under it, this guide is inserted to a depth of about 3 cm., usually between the fourth and fifth lumbar spines. The needle is then introduced through the guide and pushed forward until it enters the subarachnoid space. This guide has made the spinal puncture a more precise maneuver than before. For the uncooperative patient who bends backward instead of forward, it is very helpful.

It has also made possible the use of needles finer than would be safe otherwise. No effort is made to force a long thin needle through tough structures, and the danger of breakage is less. Most of the work has been done with needles of 0.7 mm. caliber. I found 0.5 mm. needles

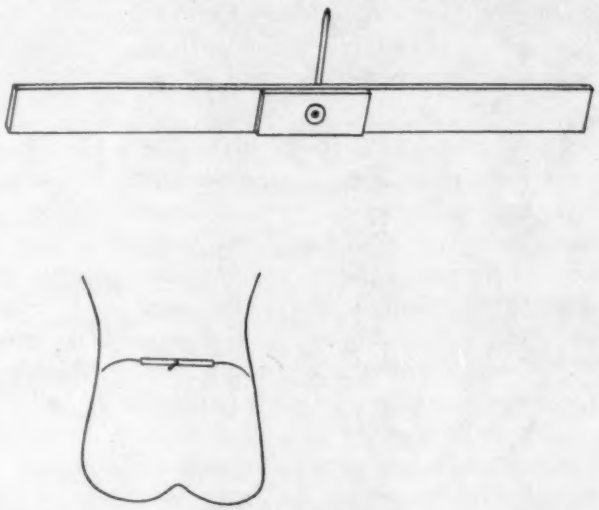

Fig. 1.—The upper figure shows the guide for the spinal needle; one-half natural size. The lower figure shows the method of use.

impracticable, because spinal fluid will scarcely flow through so fine a needle, and it was often impossible to tell when the subarachnoid space had been entered. I now use 0.6 mm. needles with much satisfaction.[1]

The wound in the dura made by such a needle is trifling. Tested on the cranial dura of a sheep, needles with a long cutting point make a hole which is a simple slit. Needles with a short bevel make a slit that is slightly curved. Holes made with the needles described have to be studied with a magnifying glass. They show the same characteristics as larger ones, but are so tiny that it is impossible to credit them with giving exit to any significant amount of spinal fluid before healing.

1. All of this instrumentarium can be secured from C. G. Heynemann of Leipzig, Germany.

The only way I could make a trap door opening was by forcing the dull sheath of a trocar through the dura. This leaves a rent, shaped like a half circle, from each end of which extends a short tangent.

2. *The Drug Used.*—Benzoyl-dimethyl-aminoethylpropanol hydrochloride (stovaine) has been abandoned as a local anesthetic because of its irritant properties. A 5 per cent solution injected into the skin can cause complete necrosis.[2] However, it has come to be used widely as a spinal anesthetic, and commonly in a 5 per cent solution, which is somewhat diluted, of course, in the process of injection. My limited experience with it has not been pleasant. It caused a number of severe paralyses of the bladder. One of the patients returned home with his control permanently impaired. Procaine hydrochloride and tutocain seem free from such dangers. Tutocain has caused fewer headaches than procaine hydrochloride, but is not entirely reliable. In one of ninety-three cases it failed to produce anesthesia. I regard procaine hydrochloride as the anesthetic of choice.

3. *The Localization of the Anesthesia.*—Injected into the subarachnoid space as a simple solution, the anesthetic diffuses somewhat capriciously. Its distribution can be more accurately controlled if it is contained in a heavy viscid medium. The viscidity of such a solution maintains its individuality, and its weight makes possible the shifting of the solution to any desired point in the dural sac by change in the patient's position. I have worked with solutions of dextrose and of cane sugar. Colored with methylene blue (methylthionine chloride, U. S. P.), either solution can be seen to maintain its individuality for hours when placed at the bottom of a glass of water.

The injection of such a solution through a fine needle introduces some complications. The process can be observed in a test tube. With a needle bent at its tip to a right angle, the solution can be injected against the side of the tube. It settles to the bottom of the test tube and is diluted to double its original volume, if the injection has been slow and careful. Injection under high pressure increases the degree of dilution. On coloring the water in the test tube and injecting the anesthetic solution clear, it is found that about a third of the injected solution remains unmixed and of its original strength. This means that when fine needles are used in practical work, about one sixth of the solution in the dural sac is of the original strength, and above this floats a diluted solution the uppermost fraction of which is doubtless very weak.

When injected against the smooth side of a test tube, the resulting dilution is fairly constant. When injected into the spinal canal against

2. Braun, H.: Lokalanesthesis, ed. 3, Leipzig, Johann Ambrosius Barth, 1914, p. 133.

the irregular surface of the cauda equina, the resulting dilution is very inconstant, and efforts to govern the height of the anesthesia by injecting volumes calculated to fill the dural sac to different heights have not been successful. To illustrate, 5 cc. of an anesthetic solution was injected between the fourth and fifth lumbar spines in each of three successive patients. The first showed an anesthesia of the anal region, together with a small saddle-shaped area of the adjacent skin. In the second patient, the anesthesia included the lower limbs and the penis. An internal urethrotomy caused no pain. In the third patient, sensation was dulled but not altogether abolished at the middle of the thigh.

This considerable and uncertain dilution of the injected solution is due largely to the fine needle used. With coarse needles and very slow injections, the resulting volume would doubtless be fairly constant, and it might be practicable to govern the extent of the anesthesia by injecting suitable volumes of fluid. I have made no efforts in this direction, because it is easier to locate the solution, and thereby govern the extent of the anesthesia, by adjusting the table on which the patient lies. Barring some exceptional contraindication, the injection is made between the fourth and fifth lumbar spines. The table is tipped up enough to ensure a flow of the solution toward the head, and the patient's head and shoulders are placed on a pillow the height of which governs the point where the solution remains.

From the standpoint of the anesthesia, operations divide themselves into three classes: The first class is made up of those requiring an anesthesia of the perineum and adjacent skin only. Pitkin and his colleagues have used this type of anesthesia successfully in obstetrical cases. I use it for hemorrhoidectomies, excisions of fistulas, etc. Such patients are operated on in perfect comfort, and afterward walk somewhat unsteadily to bed. One cubic centimeter of the solution is allowed to sink to the bottom of the dural sac, and produces the anesthesia. In my experience, 0.5 cc. has been insufficient.

The second class of operations is made up of those requiring an anesthesia extending only to the umbilicus. The patients are given a pillow 8 inches (20.32 cm.) high, with a slanting support for the back 12 inches (30.48 cm.) long. This is usually satisfactory, though some later adjustment is sometimes required.

Most of my operating has been done with this type of anesthesia. It leaves little to be desired for amputations of the lower limbs, hernias, suprapubic operations on the bladder, appendectomies, etc.

The third class of operations consists of those requiring an anesthesia of the upper part of the abdomen. In such cases, the skin must be anesthetized up to the nipple line. Such patients use a lower pillow, 5 or 6 inches (12.7 or 15.24 cm.) high, and a slanting support for the back about 8 inches long.

4. *The Duration of the Anesthesia.*—One of the greatest defects of spinal anesthesia has been its short and somewhat capricious duration. Previous to this year, I never felt certain of more than half an hour to work in, and on occasion I have had to fall back on general anesthesia within twenty minutes. Surgeons with a better mastery of the method were apparently fairly certain of from fifty minutes to an hour. It would appear from the literature that this is still more or less the situation. If spinal anesthesia is to have any great usefulness, the period must be extended, for the whole current of surgical progress is toward more painstaking and careful, and therefore longer, operations.

To meet the needs of this clinic, three solutions have been developed. First, a solution for operations lasting half an hour or less. In such cases, I use 0.05 Gm. of benzoyl-dimethyl-aminoethylpropanol hydrochloride or tutocain in 1 cc. of a 5 per cent solution of dextrose. This can be depended on for half an hour's anesthesia; it seldom lasts much longer. I use this solution when operating for hemorrhoids, for the excision of anal fistulas, for opening abscesses, etc. The total number of such operations is considerable, and in this limited field such anesthesia is exceedingly satisfactory. Of late I have eliminated benzoyl-dimethyl-aminoethylpropanol hydrochloride in this work.

Theoretically, this duration of half an hour may be due to two factors. It may take thirty minutes to absorb the solution, the anesthesia ceasing when the solution is gone, or conceivably the solution may be absorbed more quickly than this but may leave the drug fixed in the nervous tissues, its effect lasting until it is oxidized or otherwise eliminated. It seemed possible to determine this point. A patient who was anesthetized to the nipple line was put to bed in a semi-sitting position. Within ten minutes the line of anesthesia had descended to the umbilicus. Terminated as is to be described, an anesthesia produced by tutocain may begin to fade in even less time that that. I concluded that the duration of the anesthesia produced by tutocain is only slightly due to fixation of the drug in the tissues, and that practically the anesthesia lasts as long as the nerves involved are bathed in the solution and no longer.

This seemed to simplify the problem of a longer anesthesia. The quantity of the dextrose solution was increased to 5 cc., and in the hope that absorption might be delayed, its concentration was raised to 10 per cent. The dose of tutocain was increased to 0.1 Gm. This solution of 5 cc. of a 10 per cent solution of dextrose, in which is dissolved 0.1 Gm. of tutocain, justified my hopes. The anesthesia resulting from its introduction has never failed to last an hour and a quarter, and usually it lasts an hour and a half. I have seen no evidence of meningeal irritation following its use.

Most of the year's operating has been done with this solution, and it has given great satisfaction. For hernias, appendectomies, amputa-

tions, work on the bladder, etc., the time afforded is adequate, even though the operator gives the anesthetic solution himself before scrubbing up, and thus the first fifteen minutes of the anesthesia are lost.

This solution is satisfactory for most operations, but not for all. Splenectomies, work on the bile ducts, severe gastric operations, etc., are done infrequently, but double hernias are common, and they require a longer period of anesthesia than this solution affords. In the effort to lengthen the anesthesia further, the use of tutocain was stopped and that of procaine hydrochloride was begun. This drug apparently becomes fixed in the nervous tissues when used as a spinal anesthetic. In such an experiment as that described, after elevation of the head, the anesthetic level does not drop until after about twenty or twenty-five minutes.

Cane sugar was also used in the place of the dextrose, in the hope that its larger molecule might make absorption slower. Procaine hydrochloride is only about half as powerful an anesthetic as tutocain, but it is perhaps three times less toxic. I therefore felt safe in raising the dose to 5 grains (0.324 Gm.). This solution, 5 cc. of a 10 per cent solution of cane sugar in which 5 grains of procaine hydrochloride is dissolved, also proved a success. The anesthesia resulting from its introduction can be depended on for two hours and usually lasts a little longer.

For a prolonged anesthesia of the upper part of the abdomen I do not inject the solution through a 0.6 mm. needle. When such a needle is used, the upper zone of anesthesia may last from only an hour to an hour and a half, while the lower zone persists to the full expected time. The reason for this is undoubtedly the character of the dilution caused by injection through a very fine needle. This has been discussed. I have had no such trouble when using 0.7 or 0.8 mm. needles.

The demands of this clinic are satisfied by these three solutions, and no effort has been made to develop anything further. It is possible that a new local anesthetic recently introduced in Germany may provide anesthesias lasting five and six hours, if its use as a spinal anesthesia proves safe.

During the past year I saw two patients whose anesthesia lasted for hours in a somewhat alarming way. Although they seemed none the worse for the experience, it was disquieting. Much more often I see patients whose condition makes it desirable to terminate the anesthesia as promptly as possible after the operative work has been finished. These, of course, are the patients whose blood pressure has not been stabilized adequately. I have found that a spinal anesthesia can be terminated very simply by injecting 4 ounces (118.4 cc.) of a 5 per cent salt solution intravenously. This idea comes from Dr. Cushing's clinic, where the same thing is done to reduce intracranial pressure. Anesthesia

produced by tutocain begins to fade within five minutes after such an injection, and rapidly disappears. I have had occasion to use this procedure in four such cases, with uniform success. Anesthesias produced by procaine hydrochloride begin to fade after from twenty to twenty-five minutes, and within the following twenty minutes sensation returns over the upper part of the anesthetic area. When 4 ounces of the solution is used, the lower part of the anesthetic area, especially the legs and feet, regain their sensation more slowly. When 8 ounces (236 cc.) is injected or the percentage is raised to 10, the effect is more rapid, but in two cases in which this was done the reaction following was severe. I have had occasion to terminate an anesthesia produced by procaine hydrochloride in this way nine times, and have found the procedure valuable.

These results suggested that the injection of 4 ounces of distilled water just before inducing spinal anesthesia might prolong its duration, but in the single case in which the experiment was tried it completely failed to have any such effect.

5. *Stabilizing the Blood Pressure.*—Up to this time the effort to stabilize the patient's blood pressure while he is under a spinal anesthetic has been associated with and somewhat handicapped by the effort to prevent respiratory paralysis, which it is assumed will occur if the anesthetic solution reaches and paralyzes the phrenic nerves. It would seem obvious that this might occur. The solutions used paralyze the muscles of the lower limbs and of the abdominal wall. It is true that this motor paralysis is frequently incomplete. Evidently the sensory nerves are more readily affected by the solution than the motor nerves. But the motor roots are involved in all cases. If they were not, the patient could walk back to bed. The danger would seem to be self-evident, and moreover, at the best, the diffusion upward of the anesthetic is under imperfect control. The surgeon lacking all apparatus for maintaining artificial respiration has the feeling that he is walking on the edge of a precipice.

Apparently the self-evident conclusion is wrong. Le Riche and Labat have long since interpreted these cases of "respiratory paralysis" as cerebral anemia due to low blood pressure. Far more convincing is the recent work of Koster and Kasman,[3] who showed that a 2.5 per cent solution of procaine hydrochloride applied to the medulla of a cat has no influence on the respiratory movements. Two and one-half per cent is a strong solution, and if this work is confirmed and it can be determined that the human tissues are no more susceptible than those of the cat, there would seem to be no reason why plastic operations on the nose cannot be done easily and safely under spinal anesthesia. In

3. Koster, H., and Kasman, L. P.: Surg. Gynec. Obst. **49**:617 (Dec.) 1929.

this clinic, work is done with a 6 per cent solution of procaine hydrochloride, and after injection a fraction remains at that strength, while most of it must be above the 2.5 per cent used by these authors. It seemed worth while to ascertain what effect such a solution might have when applied to the medulla.

Two goats weighing 42 and 30 pounds (19.1 and 13.6 Kg.), respectively, were each given intraspinally 4 cc. of a 10 per cent solution of cane sugar in which was dissolved 4 grains of procaine hydrochloride. They were immediately hung up by the heels, and remained suspended for five minutes, after which time they were laid on the floor. Both of these animals showed complete paralysis of their hind legs, and nearly complete paralysis of their forelegs. Their voices were almost lost so that they could bleat only in a sort of a whisper. The entire body, including the face, was anesthetic, with the exception of the ears, which remained unaffected. Respirations were quiet and with the animal lying motionless on the floor were shallow, but pinching the ear with a hemostat gave rise to active and exaggerated respirations. After about an hour and a half the animals got up and stood on their feet more or less unsteadily, and shortly thereafter the effects of the anesthetic disappeared. A 10 pound (4.5 Kg.) gazelle that was given 2 cc. of this solution died after a suspension of three minutes. He died in the midst of spasmodic, irregular movements and apparently not from primary respiratory paralysis. It would seem that the danger of respiratory paralysis is not so immediate as was supposed. It will doubtless be possible to work out this point accurately and to eliminate all risk of respiratory paralysis.

The danger of respiratory paralysis may be fictitious, but the danger of falling blood pressure is not. It is this more than anything else that frightened operators away from spinal anesthesia in the past. The present revival of its use is due largely to the introduction of ephedrine, which has gained wide use as a stabilizer of the blood pressure in these cases.

Anesthesias confined to the perineum have no effect on the blood pressure. In thirty-four such operations, I have had no trouble. When the anesthesia reaches to the umbilicus, the patient's blood pressure requires some stabilizing. For these cases, I use from ¾ to 1 grain (0.0486 to 0.065 Gm.) of ephedrine, given subcutaneously just before the operation. This answers the purpose very well. Of eighty-three such cases only one required some epinephrine to reinforce the blood pressure during the operation.

Work in the upper part of the abdomen, however, still presents serious problems. To abolish sensation completely the fourth thoracic

segment must be reached, and the skin up to the nipple line will be made insensitive. The whole splanchnic area and everything below it have their vasomotor tone abolished, and it is necessary to supply some adequate external vasoconstrictor stimulus for the whole period during which nervous control is lacking. Up to the present time this has been only imperfectly accomplished. The year's experience included fifty-eight anesthesias reaching to the region of the nipple line. Fifteen of

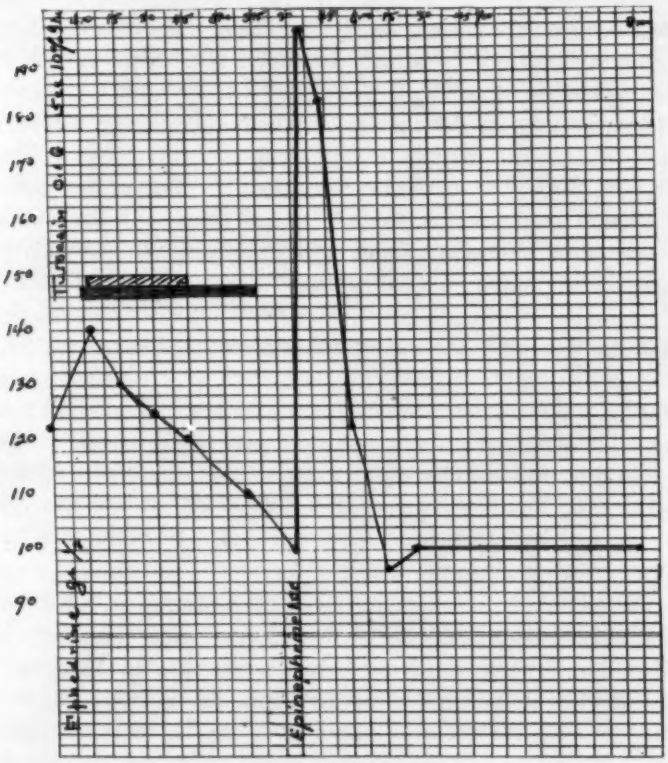

Fig. 2.—Record of the effect of anesthesia during operation for partial amputation of a foot, Feb. 28, 1929. Epinephrine was given to check a threatening drop in the blood pressure. In this and the succeeding figures, the solid shading shows the anesthetic period; the partial shading, the operative period.

these patients vomited during the course of the operation, and four more suffered from nausea. The systolic blood pressure was usually about 60 mm. when vomiting occurred. Many of the remainder suffered from a marked drop in the blood pressure. None of these patients died, but it cannot be supposed that such drops in blood pressure are matters of indifference. Adequate means of supporting vascular tone must be developed so that the blood pressure curve will remain normally flat.

I have been unable to discover any method by which ephedrine will accomplish this. Neither massive initial doses nor repeated smaller doses will carry a patient with a high spinal anesthesia through a long operation safely. Epinephrine is a much more powerful drug. I have met no situation in which it was incapable of raising the blood pressure. Figure 2 is an illustration of this capacity. Obviously a drug that can elevate blood pressure in this way is capable of maintaining it, if a

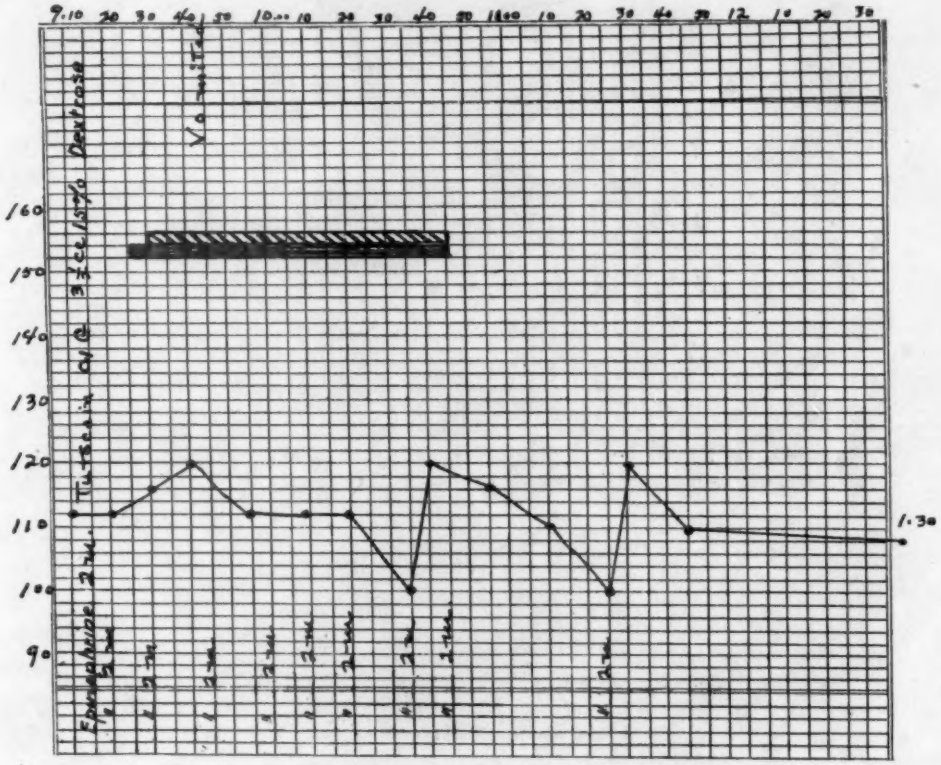

Fig. 3.—Record of the effect of anesthesia during a difficult operation for hernia, March 27, 1929. Anesthesia extended to the umbilicus. The patient was extremely nervous, and fainted during the spinal puncture. There was a tendency to a fall in blood pressure, due probably to the extreme mental reaction. The situation was controlled fairly well by the administration of epinephrine.

suitable method of administration can be devised. Epinephrine seems to be the agent needed.

The problem of administration, however, is difficult. Figure 2 illustrates not only the power of this drug, but its exceedingly precipitate and brief action. However, its action seems to last for ten minutes, so that a series of experiments was run in which the blood pressure was

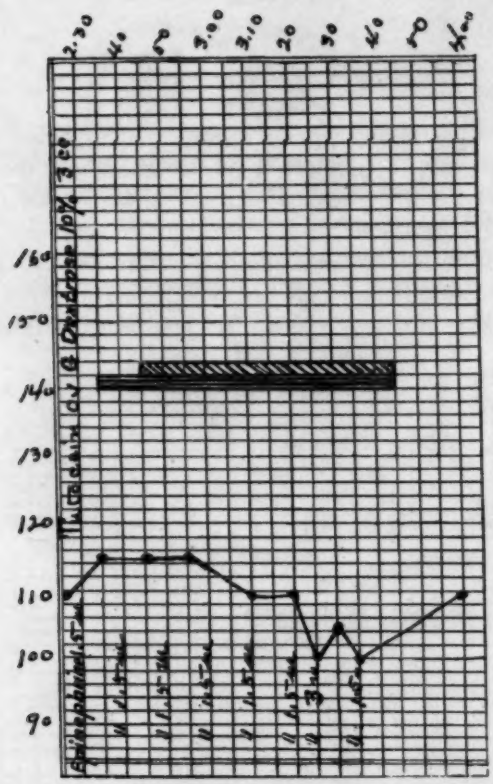

Fig. 4.—Record of the effect of anesthesia during splenectomy, April 19, 1929. Anesthesia of the diaphragm was not complete. The blood pressure was controlled fairly well by the use of epinephrine.

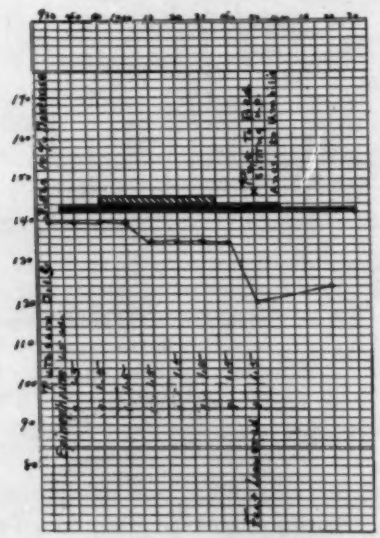

Fig. 5.—Record of the effect of anesthesia during an operation for hernia, April 25, 1929. Anesthesia extended to the nipple line. The legs were moderately elevated throughout the operation. The drop in blood pressure, which occurred when the legs were lowered, is well shown. On assuming the sitting posture, the anesthetic level dropped within ten minutes. The control of blood pressure by epinephrine was fairly effective.

maintained by the injection of 1.5 minims (0.09 cc.) of epinephrine (the commercial 1:1,000 solution) every ten minutes. This was a great improvement, and gave some encouragingly flat blood pressure curves. If the routine dosage proves inadequate, it is a simple matter to increase it. Some irregularities in results apparently were due to capricious absorption from the subcutaneous tissue. I have come to prefer the

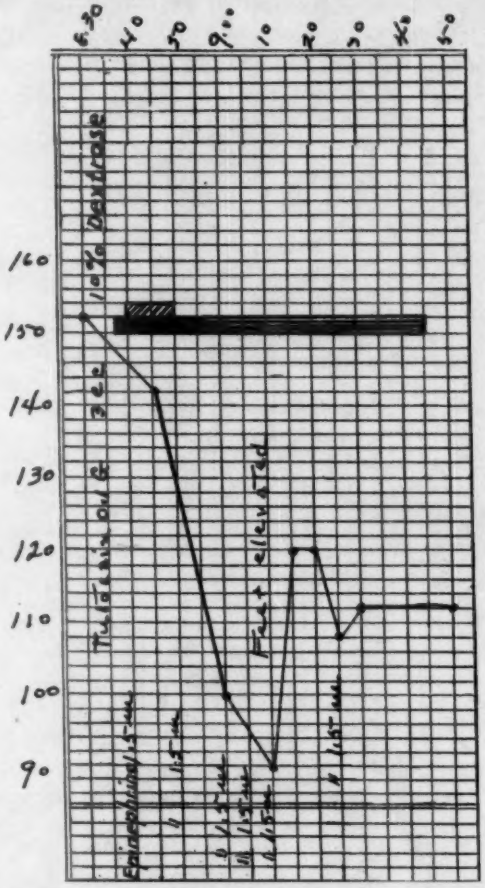

Fig. 6.—Record of the effect of anesthesia during the clamp and cautery operation for hemorrhoids. The patient was improperly placed. Anesthesia extended to the nipple line. The control of the blood pressure by epinephrine was very poor until the legs were elevated.

intramuscular administration of this drug. Figures 3, 4 and 5 are illustrations of results secured by the administration of epinephrine in this way.

There are some cases in which this method fails to control the blood pressure adequately. In these I have found it of great assistance to

elevate the feet of the patient. The operation is not embarrassed by this procedure. The head and trunk are left undisturbed. Epinephrine plus elevation of the lower limbs has controlled every situation that I have encountered. Figure 6 is the record of such a case.

Profiting by what I have learned of the ability of cane sugar to retard absorption, I ran a small series of experiments in which the blood pressure was maintained by the injection of 1 cc. of epinephrine dissolved in 5 cc. of a 10 per cent solution of cane sugar. One half of the solution was injected subcutaneously and one-half intramuscularly. This procedure appears to control the blood pressure reliably for one

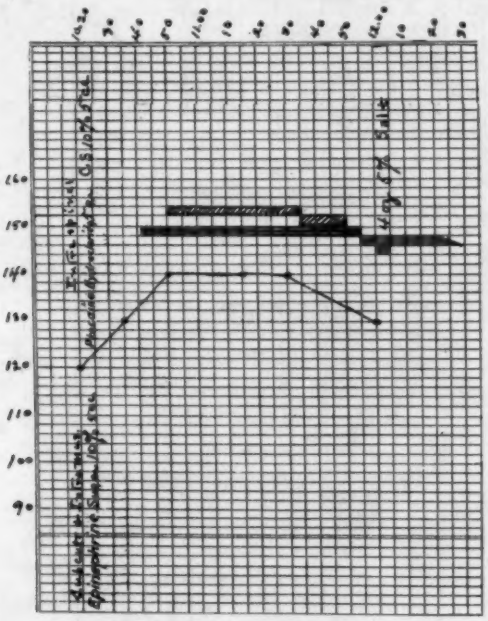

Fig. 7.—Record of the effect of anesthesia during an operation for hernia in the reclining position, and the clamp and cautery operation for hemorrhoids in the semisitting posture, Jan. 8, 1930. There was a descent of the anesthetic level from the umbilicus to the pubic region within twenty minutes after a change in position. The anesthesia was terminated by the intravenous injection of 4 ounces of 5 per cent salt solution. The blood pressure was controlled by 1 cc. of epinephrine. Absorption was spread over an hour by means of cane sugar.

hour. At the end of that time, the dose should be repeated. With this method also, there are certain cases that require elevation of the legs. My experience with this method is small as yet, but it seems to promise well. Figures 7 and 8 are charts from such cases.

The repository injections recently reported by Strauch will probably eventually provide just what is needed. By emulsifying epinephrine in

a carefully adjusted medium, he was able to distribute its action over as long a period as was desired. When this method is ready for general use, the problem of stabilizing the blood pressure during spinal anesthesia will probably cause no more trouble.[4]

6. *Postanesthetic Complications.*—I have been able to deal fairly well with the situations arising in the course of a spinal anesthesia. Postanesthetic complications have given me more trouble; vomiting is the most frequent. Sometimes it is due to a faulty solution. On a trip

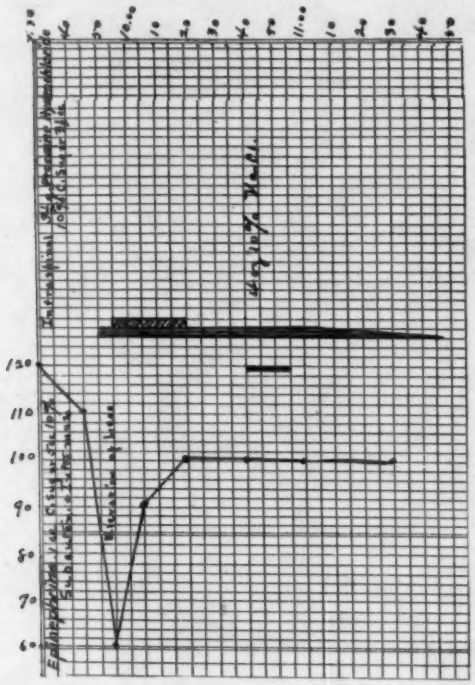

Fig. 8.—Record of the effect of anesthesia during an internal urethrotomy, Dec. 26, 1929. There was an unexpected diffusion upward. Anesthesia extended 3 fingerbreadths above the nipple line. Anesthesia was terminated by an intravenous injection of salt solution. The blood pressure was controlled by 1 cc. of epinephrine in 10 per cent solution of cane sugar. The control was very poor until the legs were elevated.

to an outlying district 50 per cent of the patients vomited after the anesthesia. Investigation showed that the distilled water had been run through some old rubber tubing, and the injected solutions were very acid in reaction. A drop of 5 per cent sodium carbonate solution reduced the vomiting to a small fraction of its previous frequency.

4. Stranch, C. B.: Repository Injections, J. A. M. A. **92**:1177 (April 6) 1929.

Headache is also troublesome, and is usually associated with vomiting. Excluding the period when I was working with solutions that were obviously unsuitable, headaches occurred in about one case in ten. They usually last less than twenty-four hours, and are amenable to acetylsalicylic acid. Severe pains in the limbs occurred in one case.

I find it difficult to believe that these headaches are due to leakage of spinal fluid through a large puncture wound in the dura. I have always used 0.7 mm. needles in this work. In the days when I used a simple solution of procaine hydrochloride, headaches were frequent and severe. I use the same needle now and the same drug, but in a heavy solution of cane sugar or dextrose, and with attention to the reaction of the injected solution. Headaches occur now in perhaps 10 per cent of the cases and are of a mild type. The use of 0.5 mm. needles did not reduce their frequency.

Two rather distressing fatalities taught me that some impairment of vasomotor tone lasts for a considerable time after the anesthesia has disappeared. Two women with enormous ovarian cysts entered the clinic and were operated on during the same afternoon. One of the cysts weighed 56 pounds (25.4 Kg.); the other was estimated at 40 (18.1 Kg.). In each case the abdomen was under marked tension. Such cases are fairly common in Arabia. During the past fifteen years the members of this clinic and their immediate neighbors have seen perhaps twenty cases. Barring adhesions, the removal of such a cyst is easy. None of the patients has needed treatment for postoperative shock. These two women were operated on under tutocain anesthesia, 0.1 Gm. in 5 cc. of 10 per cent dextrose solution. Ephedrine, 1 grain, was given beforehand. Severe shock developed after the operations, in seven hours in one patient and in twenty hours in the other, and they died. Since this experience, I have regarded it as probable that some impairment of vasomotor tone lasts at least through the first twenty-four hours after a spinal anesthesia. I regard as unsuitable for such anesthesia cases in which the operation in itself leaves a damaged vasomotor tone. To add to such damage the further impairment of spinal anesthesia is dangerous.

COMMENT

I have come to regard spinal anesthesia as the procedure of choice for surgeons working in the jungle, as well as for those in large centers. There is still, however, a good deal of work to be done in perfecting this method of anesthesia, and the experience of many observers will have to be assembled before all of the questions concerning it are answered.

THE ETIOLOGY OF NEOPLASMS OF THE BREAST

WITH NOTES ON THEIR RELATION TO OTHER TUMORS OF THE REPRODUCTIVE SYSTEM

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NEW YORK

(Concluded from Page 443)

CLINICAL STUDY

The following pages contain a report of the results of a study of 271 women who entered the Memorial Hospital primarily on account of some form of neoplastic disease of the breast. The special object of the analysis of these cases is to afford a rough test of the fitness of the conceptions derived from the preceding theoretical discussion for explaining the origin of a series of typical breast neoplasms. The material used, although relatively small, has been examined with considerable care and it is felt that such an approach by means of a detailed study of a few cases is essential in what must be looked on as a preliminary survey of a rather new field.

The entire group of cases came under my direct observation while the patients were attending one of the outpatient clinics at the Memorial Hospital. The majority were questioned and examined during their first visit to the hospital. When it became evident, however, that this group of patients was yielding a relatively small number of cases in which pathologic specimens were eventually becoming available, about 100 patients were added to the list from the follow-up clinic of the breast department.

CLASSIFICATION

The general failure of statistical studies to lead to any definite conclusions on the nature of the exciting agent in tumors of the breast may be attributed to the fact that these statistics have invariably been based on a mass of unsorted material. In this paper, therefore, an attempt will be made to classify the cases into groups as morphologically homogeneous as possible and further to subdivide these according to the physiologic condition of the breast under which the tumor appears to have originated.

Morphologic Classification.—(*A*) Benign Tumors: One hundred and fifteen benign tumors are included in the study. The examination of the nonmalignant forms is useful, for these forms are at least par-

tially classifiable and the obvious differences in the etiologies of fibro-adenomas and chronic mastitis make apparent the possible differences in origin that may exist in various malignant forms.

(1) Fibro-adenomas, characterized by being sharply circumscribed and having histologically a high degree of organization.

(2) Painful nodules, the lesion regarded by Moszkowicz as closely related to and possibly the precursor of the fibro-adenoma and shown by Sebening to consist of circumscribed areas of hyperplasia. Cases of this condition are often loosely classified by clinicians as "chronic mastitis," and indeed, in practice, the disease is difficult to delimit from the fibro-adenomas on the one hand and from the diffuse hyperplastic processes on the other.

(3) "Chronic mastitis," characterized essentially by a diffuse hyperplasia of the breast epithelium. Under this head have been placed certain cases exhibiting a minor degree of localization of the process as well as the completely generalized lesions.

(4) Papillary growths, represented in this study by a few cases of intraductal papilloma and papillary cystadenoma. The number of cases was too small to permit further subdivision.

(*B*) Carcinoma: Criteria are almost entirely lacking for a classification of cases of cancer of the breast from a genetic standpoint. Two theoretical means of genetically subdividing such cases will be considered. In the first place, there is a definite possibility that certain cancers, particularly those in younger women, are derived from or under similar circumstances to the fibro-adenomas, whereas a second group may arise in similar relation to chronic mastitis. The other point of approach is through the study of the different histologic types of cancer of the breast to which special reference is made later.

The assignment of a given case to any particular morphologic category has in many instances in the present paper been accomplished on purely clinical grounds since the majority of patients with benign tumors were not considered to require operation and a number of those with malignant growths received only radiation therapy. The latter were advanced or recurrent and there can be little doubt of the diagnosis.

It must be noted finally that in the study of tumors one is actually concerned with at least two problems, the origin of neoplasms in general and the reasons for their occurrence in, or evolution through, various stages of cellular undifferentiation. In general, in the following study the divergences from the normal that are common to both benign and malignant tumors are best interpreted as instrumental in the production of neoplasms in general, while differences between statistics on the benign and the malignant series should, theoretically, give a hint to the conditions which produce the variations in cellular differentiation.

Physiologic Classification.—An age classification is nearly essential in the clinical study of tumors for the factor of elapsed time since the period of activity of a hypothetic etiologic agent is most important in evaluating its possible effectiveness in the production of the tumor. Lactation accidents probably have less relation to cancer in women at the age of 70 than at 40 years. Such a classification is of special importance in the breast for in this organ a sharp line is drawn at the menopause marking a complete anatomic and physiologic transformation which is so fundamental that the effects of many previous abnormal stimuli must entirely lose their significance after the change is complete. A history of abnormal menstruation has an entirely different value depending on whether it is found in the present history of a woman developing cancer at 30 or in the past history of a patient with cancer at 60.

The classification adopted which depends on the theoretical state of the ovarian function is as follows:

A_1. Women from puberty to the age of 35 in whom a normal ovarian function should be expected.

A_2. Women from 35 up to 40 years of age, in whom a decline in ovarian activity may be beginning, although evidence of this decline is not to be expected in the normal woman.

B_1. Women over 40 in whom menstrual irregularities have not yet appeared but in whom some physiologic decline in ovarian activity may be assumed.

B_2. Women over 40 who were showing menstrual evidence of approaching menopause at the time of or within a year after the detection of the tumor and those whose final period had occurred less than six months before the detection of the tumor.

B_3. Women over 40 who have ceased to menstruate for from six months to five years, in whom some ovarian activity is probably still present.

C_1. Women from five to ten years past their menopause in whom the effect of the ovary on the breast must at most be a very indirect one.

C_2. Women whose last period lies over ten years behind them in whom ovarian activity has long been apparently extinguished.

In most of the tabulations to be presented, the cases have been recombined into three major physiologic groups, A, B and C, or premenopausal, intramenopausal and postmenopausal, respectively. All cases have, however, been separately charted under the more complicated system, and when differences occurred that are not apparent in the combined totals they will be noted.

In order to make the time relation as accurate as possible, all ages were corrected by subtraction of the known duration from the age given by the patient on admission except in those instances in which a new growth activity had been superimposed on a quiescent tumor of long standing. Yet many growths may have had their microscopic

inception years before the apparent onset. Such a long latent period in the early history of neoplasms is perhaps especially to be considered in the study of old age tumors.

AGE INCIDENCE

The pattern of age incidence of any group of tumors has great significance, since the occurrence of a given tumor form in a special age epoch requires the consideration of a possible relationship with the disturbances of function peculiar to that period.

The age table (table 1) gives certain fundamental points:

(*A*) *Benign Tumors.*—Benign tumors are practically limited to the period of ovarian activity. This is a positive observation common to almost all statistics (Primrose, Bunts, Gross), but its immense importance is usually overlooked.

TABLE 1.—*Age Incidence*

		Premenopause		Menopause			Postmenopause	
	Totals	Under 35	35-40	40 to Menopause	Menopause	6 Mos.-5 Yrs. After Menopause	5-10 Years Postmenopause	Over 10 Years Postmenopause
Fibro-adenomas	26	18	3	2	1	1	0	1
Painful nodules	22	20	1	0	1	0	0	0
Chronic mastitis	57	22	8	3	17	4	2	1
Papillary growths	11	2	4	0	3	1	1	0
Total benign	116	62	16	5	22	6	3	2
Per cent benign		53.5	13.8	4.3	19.0	5.1	2.6	1.7
Total malignant	155	17	24	18	25	22	24	25
Per cent malignant		11.0	15.5	11.6	16.1	14.2	15.5	16.1

Fibro-adenomas occur characteristically in the very young women (McFarland) and are thus definitely associated with the developmental years of sexual activity. The statistics of Bunts show a second rise in the incidence of fibro-adenomas near the menopause, but this is possibly to be explained as an inclusion in the group of many small, somewhat localized tumors associated with chronic mastitis of the type that Bloodgood designates a nonencapsulated adenoma.

Cases of circumscribed hyperplasia (painful nodules) are found almost exclusively among the young women.

Cases of chronic mastitis are scattered. A large number appear at an early age. This group of patients had many characteristics in common with those suffering from localized painful lumps, and it is possible that a mistake was made in classifying them at all with the chronic mastitis of later years. A second concentration of cases of diffuse "chronic mastitis" occurs in very definite relation to the menopause, the great majority of the patients appearing to be actually in the years of

the "change." Statistics based on cases of chronic mastitis that have come to operation usually emphasize more definitely this high incidence in the years just before the menopause.

It is to be noted that it is the tumor with the organic structure resembling in some respects that of the normal breast that occurs in the developmental years, whereas the diffuse hyperplasia is more frequent in the regression period.

(*B*) *Carcinoma.*—There is evidence in table 1 also of a relatively high incidence of cancer of the breast in young women as compared with that of many other forms of cancer. A trifle over a fourth (26.5 per cent) of the cases occur before the fortieth year. Two-thirds (68.4 per cent) have occurred before the women have reached a point five years after the menopause and 83.9 per cent have occurred before the menopause has been passed by ten years.

These figures correspond fairly well with the figures that Lane-Claypon listed for America where the age incidence appears to be especially low, while in a collected group of 8,053 cases from many countries, Lane-Claypon's figures show a somewhat higher average age incidence.

The relative frequency of malignancy in young women is a peculiarity which the breast shares with the other organs of the reproductory system, a fact which has been commented on by many writers. Lauterborn, and later Paulsen, using a very large number of statistics, were able to point out that while before the age of 50 cancer affected women far more frequently than men, there was a gradual equalization of the ratio in the sixth decade. This early preponderance in women appeared due to the special quota of cases supplied by the reproductory organs, and as a result Lauterborn concluded that the high early age incidence of cancer in females was due to a disturbance of the internal secretory function of the sex cells. Gade, taking a slightly different point of view, ascribed the frequent development of cancer of the reproductory tract in young women to the earlier senescence of these organs as compared with those of the other body systems. It would be only a minor modification of Lauterborn's theory to suggest that cancer of the breast occurred early because the precancerous lesions from which it is derived develop during the period of ovarian activity and particularly in relation to the menopause.

Cases of carcinoma do occur in considerable number, however, many years after the benign growths have become great rarities. This essential difference in etiology is emphasized by the observation that cancer appearing at the menopause is usually associated with grossly demonstrable chronic mastitis while cancer in an older woman appears usually as an isolated process in a smooth and atrophic breast. From MacCarty's statement that chronic mastitis was present in all of 1,000 cases of can-

cer of the breast, it appears that this benign process never entirely disappears, but the clinical evidence of chronic mastitis in the breasts of older women is nevertheless so slight that the microscopic observations of MacCarty may well represent mere remnants of the hyperplastic tissue formed at or before the menopause.

(*C*) *Sarcoma.*—Although cases of sarcoma do not appear in the present study, it is interesting to note that the peak of the sarcoma incidence occurs at a much lower age than does that of carcinoma (Gross), suggesting the possibility that the former tumors are especially related to the fibro-adenomas, which exhibit an early age incidence and possess often considerable connective tissue activity.

DEGREE OF BREAST DEVELOPMENT

The various estates relative to marriage and maternity are to be considered in this paper chiefly in the light of their function of producing hypertrophy of the breast, and the history of the course of lactation is to be regarded as indicative of the degree of breast development that has been attained.

(*A*) *Relation of Marriage and Pregnancy to Tumors of the Breast.*—The relation of these factors to the tumors of the present group is presented in table 2 *A*, but since reliable figures on much larger groups of cases exist it is preferable to discuss these.

In a total of 14,419 cases of cancer of the breast collected from many different sources, Lane-Claypon found 18.3 per cent single women, as compared with 11 per cent unmarried among 43,022,572 women of over 40 living in the ten countries from which the breast figures were assembled. Hoffman, Simons, Deelman and Crile have each emphasized this relative preference of cancer for the unmarried woman, and Peller attributed to pregnancy a "protective influence" against carcinoma. Lane-Claypon's own study showed the same relative frequency of carcinoma of the breast among single women and pointed furthermore to the fact that among married women the fertility in the cases of cancer was definitely less than that of the noncancerous controls.

The first cited figures, the size of which give them a reliability beyond the hope of any single series, are of tremendous significance. If lactation errors or accidents have anything to do with cancer of the breast, one must wonder why the cases so predisposed have not overbalanced the statistics in favor of the married and fertile women. Cancer of the cervix occurs about fifty times as frequently in married as in single women. Its etiology is strongly influenced by the effects of childbearing. The supporters of the belief that the inflammations and congestions incidental to childbirth are provocative of cancer of the breast have to explain in the first place the fact that the statistical

TABLE 2.—*A. Breast Development as Result of Marriage and Pregnancy*

Percentages Based on Total Women in Classes	Premenopause				Menopause				Postmenopause				Totals			
	Per Cent of Total With Children	Per Cent, Miscarriage Only	Per Cent, Married but Sterile	Per Cent, Single	Per Cent of Total With Children	Per Cent, Miscarriage Only	Per Cent, Married but Sterile	Per Cent, Single	Per Cent of Total With Children	Per Cent, Miscarriage Only	Per Cent, Married but Sterile	Per Cent, Single	Per Cent of Total With Children	Per Cent, Miscarriage Only	Per Cent, Married but Sterile	Per Cent, Single
Fibro-adenomas	23.8	0	4.8	71.4	50.0	0	0	50	(100.0)	0	0	0	30.8	0	3.8	65.4
Painful nodules	47.7	9.5	9.5	33.3	0	0	(100.0)	0	.....	...	....	.....	45.7	9.1	13.5	31.7
Chronic mastitis	76.7	3.3	6.7	13.3	79.0	8.7	8.7	4.4	(67.0)	0	0	(33.0)	77.1	5.4	7.1	10.7
Papillary growths	66.7	0	16.7	16.7	67.0	(33.0)	0	0	(100.0)	0	0	0	70.0	10.0	10.0	10.0
Total benign	53.8	3.9	7.7	34.6	67.7	9.7	12.9	9.7	80.0	0	0	20.0	58.7	5.3	7.9	27.5
Total malignant	68.2	0	9.8	22.0	76.6	0	12.6	10.8	71.5	0	12.2	16.3	72.9	0	11.6	15.5

B. Breast Development as Indicated by Functional Capacity in Lactation

Percentages Based on Total Women With Children	Premenopause				Menopause				Postmenopause				Totals			
	Per Cent Lactations Always Normal	Per Cent Lactations Sometimes Normal	Per Cent Lactations Always Subnormal	Per Cent Lactations Never Tried	Per Cent Lactations Always Normal	Per Cent Lactations Sometimes Normal	Per Cent Lactations Always Subnormal	Per Cent Lactations Never Tried	Per Cent Lactations Always Normal	Per Cent Lactations Sometimes Normal	Per Cent Lactations Always Subnormal	Per Cent Lactations Never Tried	Per Cent Lactations Always	Per Cent Lactations Sometimes Normal	Per Cent Lactations Always Subnormal	Per Cent Lactations Never Tried
Fibro-adenomas	20.0	0	60.0	20.0	(50.0)	0	(50.0)	0	0	(100.0)	0	0	25.0	12.5	50.0	12.5
Painful nodules	40.0	0	50.0	10.0	.....	....	.....	...	.....	.....	.....	...	40.0	0	50.0	10.0
Chronic mastitis	39.0	34.8	17.4	8.7	50.0	22.2	27.8	0	(50.0)	0	(50.0)	0	44.2	28.0	23.3	4.7
Papillary growths	25.0	0	75.0	0	(50.0)	0	(50.0)	0	0	0	(100.0)	0	29.0	0	71.0	0
Total benign	35.7	19.0	35.7	9.5	50.0	18.2	31.8	0	(25.0)	(25.0)	(50.0)	0	39.4	19.1	35.3	5.9
Total malignant	57.1	17.8	21.4	3.5	48.0	26.0	18.0	8.0	54.3	25.4	20.0	0	52.2	24.0	19.4	4.4

relationship here cannot compare with that existing for carcinoma of the cervix, secondly, that there is positively no greater incidence of cancer of the breast in women who have had children and finally that the reverse of what should be expected from a lactation-inflammatory theory is true, namely, that the disease is commoner in single than in married, and in nulliparous than in child-bearing women.

The apparent protective effects of marriage and childbirth may perhaps find their explanations in the following considerations: 1. The women who marry are in general more nearly normal sexually than those who have either no opportunity or no inclination to do so. 2. The physiologic effects of marriage alone and to a greater extent those of pregnancy result in the more complete maturity of the reproductory organs and the elimination of certain minor but perhaps frequent defects of development and function. 3. Sterility in particular is evidence of the existence of abnormalities of the reproductory organs, that may be congenital or acquired, and affect the breast through the ovary.

Examination of table 2 *A* reveals the following points which may be added cautiously to the conclusions drawn from the larger statistics: 1. The fibro-adenomas show a particular tendency to occur among nulliparous women. 2. The so-called "painful nodules" show a somewhat less marked tendency to occur in breasts that have never undergone pregnancy hypertrophy. 3. Cases of chronic mastitis, on the contrary, tend to occur in women who have borne children, a fact corroborative of McFarland's histologic studies on residual lactation acini but contradictory of the reports of certain other writers such as Semb. 4. In the malignant group, the proportion of women who have borne children is at all ages lower than in the chronic mastitis series and higher than in the fibro-adenomas, an observation suggestive of the possibility that cancer may sometimes be related etiologically to the localized and sometimes to the diffuse processes.

As regards both the benign and malignant tumors, relatively many more single women are affected in the early age groups than in the later. This is partly due to the higher percentage of single women at that age in the general population, but it also indicates that in young women, in particular, congenital predispositions may be especially important. For the malignant series it may indicate that in the younger age groups there are more fibro-adenoma derivatives.

(*B*) *Relation of Lactation to Tumors of the Breast.*—The importance of the function of lactation in the life history of the breast has made it an obvious field for study and many authors (Leaf, Adair, Lane-Claypon) have found an apparent relation between certain abnormalities of nursing and the development of cancer. Lane-Claypon's survey of the literature on the subject led her to no conclusions, but in her own

studies the cancer group contained a higher percentage of women who had not nursed their children (and also, paradoxically, more who had nursed their children over excessively long periods) than did her control group. She stated that the nonlactation "seems" chiefly due to disinclination on the part of the mother.

(1) Nursing Failures: In regard to the actual incidence of nursing failures among the women in this series, the following points stand out from a study of tables 2 *B* and 3. 1. If one considers the incidence of lactation failures in reference to all the children borne by the patients with tumor (table 3), it appears that 91.4 per cent of the children of women with benign and 91.7 per cent of the children of women with malignant tumors were nursed for at least a short period and that 69.3 and 77.4 per cent of the respective groups were nursed for at least six months. As a rough control for these percentages may be mentioned the report of Mitchell who found that of 3,000 normal mothers bringing their babies to the Children's Hospital in Philadelphia, 80 per cent had nursed their children for some time and 40 per cent had nursed over six months. It appears, therefore, that the nursing record in these cases of tumor has been excellent. 2. The children of the patients with cancer had been more often successfully nursed than those of any of the patients with benign tumor, but in particular more often than those of patients with fibro-adenoma and "painful nodules." 3. There was scarcely any difference in the incidence of nursing failures in the young as compared with the older cases of cancer.

(2) Causes of Nursing Failure: According to the special theory of tumor genesis which one has in mind, one may evaluate the history of breast behavior during lactation in terms of congestion and stasis or of development and functional capacity. On account of this divergence in point of view, it is of great importance to note that in the present group of women, by far the commonest cause of failure to nurse normally for at least six months was insufficient milk supply, i. e., inherent physiologic deficiency (table 3). Next to this reason in order of frequency come infantile causes, including stillbirths, then maternal illness, including new pregnancy. Weaning on account of local breast trouble, usually abscess, accounts for a few cases, while the number of children deliberately not nursed, when the physiology of the breast and the health of mother and child permitted it, is almost negligible. About 2 per cent of all children of all groups were thus deliberately refused the breast by the mother.

3. Nursing Capacity: Since it is clear that at least among the women now under consideration refusal to nurse played essentially no part and a physiologic deficiency was the chief cause of failure to nurse properly, it is necessary to consider in special detail the factor of underdevelopment as manifested by hypogalactia. An idea of the normal incidence

TABLE 3.—*Causes and Types of Lactation Deficiencies*

	Premenopause: Puberty to 40													Menopause: Age 40 to 5 Years after Cessation										
			No Lactation					Lactation Under 6 Mos.							No Lactation					Lactation under 6 Mos.					
	Total Children	Per Cent Normally Nursed	Lack of Milk	Infant Death or Disease	Maternal Illness	Breast Disease	Economic or Dis-inclination	Failure in Supply	Infant Death or Disease	Maternal Illness	Breast Disease	Economic or Dis-inclination	Complement Feedings	Total Children	Per Cent Normally Nursed	Lack of Milk	Infant Death or Disease	Maternal Illness	Breast Disease	Economic or Dis-inclination	Failure in Supply	Infant Death or Disease	Maternal Illness	Breast Disease	Economic or Dis-inclination	Complement Feeding Cases
Fibro-adenomas ...	9	11	0	1	0	0	0	6	0	0	0	0	1	4	50	0	0	0	0	0	2	0	0	0	0	0
Painful nodules....	13	54	1	1	0	0	0	4	0	0	0	0	0	0	..	..	..	..	..	..	..	..	..	..	..	..
Chronic mastitis....	51	55	1	2	4	0	0	5	2	3	1	1	4	60	75	0	1	0	0	0	6	1	1	0	1	5
Papillary growth...	8	25	0	0	0	0	0	1	0	0	0	0	5	6	67	0	1	0	0	0	1	0	0	0	0	
Benign	81	47	2	4	4	0	0	16	2	3	1	1	10	70	73	0	2	0	0	0	9	1	1	0	1	5
Malignant	66	65	3	0	2	1	0	13	0	0	0	0	4	146	74	4	6	0	2	1	8	2	4	1	5	4
	Postmenopause: Over 5 Years Since Cessation													Total												
Fibro-adenomas ...	7	86	0	0	0	0	0	0	0	1	0	0	0	20	45	0	1	0	0	0	8	0	1	0	0	1
Painful nodules....	0	..	.	.	.	.	.	..	.	.	.	.	..	13	54	1	1	0	0	0	4	0	0	0	0	0
Chronic mastitis....	4	75	1	0	0	0	0	0	0	0	0	0	0	115	66	2	3	4	0	0	11	3	4	1	2	9
Papillary growths..	1	0	0	0	1	0	0	0	0	0	0	0	0	15	40	0	1	1	0	0	2	0	0	0	0	5
Benign	12	75	1	0	1	0	0	0	0	1	0	0	0	163	60	3	6	5	0	0	25	3	5	1	2	15
Malignant	137	72	4	2	2	0	2	12	1	2	1	1	11	349	72	11	8	4	3	3	33	3	6	2	6	19

Summary:

Per cent of deliveries not followed by any nursing period: benign, 8.6; malignant, 8.3.

Per cent of deliveries followed by a nursing period of at least six months: benign, 69.3; malignant, 77.4.

Per cent of deliveries followed by subnormal nursing function, exclusive of cases merely requiring complementary feeding: Primary hypogalactia: benign, 1.8; malignant, 3.1. Secondary hypogalactia: benign 15.3; malignant, 9.4.

of this condition is given by Landé's figures which showed that of 807 women, 4.5 per cent were unable to nurse at all (primary hypogalactia) and 11 per cent failed within three months. Other writers give somewhat higher figures (Coerper and Werner, Kahn, Winternitz).

A consideration of the incidence of hypogalactia among these women with tumors of the breast shows the following: 1. The total incidence of hypogalactia did not differ greatly from the apparent normal incidence, for the figures for the tumor series were as follows: Primary hypogalactia, benign, 1.8 per cent; malignant, 3.1 per cent; secondary hypogalactia, benign, 15.3 per cent; malignant, 9.4 per cent. 2. There is no reason to believe from the history of their function that the breasts of patients with cancer were inferior developmentally to the benign group, for (*a*) in table 2 *B* it is clear that the percentage of women with carcinoma of the breast who, when they made the attempt, were always able to nurse their children is considerably higher than for any of the benign groups, although (*b*) if one omits the women in whom a full lactation was accomplished at least once, then the number of women in whom complete breast maturity was possible (or in whom on at least one occasion satisfactory drainage was established) is almost exactly the same for all carcinomas and for the cases of chronic cystic mastitis. 3. The cases of fibro-adenoma and "painful nodule," however, give evidence of a probably inherent factor of subnormality by the consistent failure of the breasts of these women to give a proper supply.

Summary on Lactation.—There is no clinical evidence that the refusal of the mother to nurse has any relation to development of tumors of the breast. There is a little evidence to point toward the belief that women who have a physiologic incapacity to nurse may be particularly predisposed to the development of fibro-adenomas and certain forms of hyperplasia.

PREVIOUS BREAST DISEASE

(*A*) *Engorgement in the Puerperium.*—Statistics on this subject are perhaps of little value for moderate engorgement of the breast is a practically normal incident at the onset and termination of lactation, and it is also not clear whether its occurrence in a severe form is to be regarded as significant as a sign of special breast constitution or important as evidence that the breast has been subjected to a period of noninfectious inflammation.

The figures as obtained in this study appear in table 4. There is no apparent difference in the frequency of this condition in the benign and malignant conditions, but in each the history of engorgement is more common in the young women with tumors than among the older.

(*B*) *Mastitis Puerperalis.*—The figures in table 4 show an apparent incidence of mastitis (suppurative and nonsuppurative) of 7.9 per cent

of all the lactations of the benign group of cases and 7.1 per cent of the malignant. There is thus apparently no reason to believe that inflammation has anything to do with malignancy as opposed to tumors in general.

As compared with the apparent normal incidence of mastitis, these figures are definitely high. Weber cited the statistics from various modern clinics as varying from 0.64 to 1.93 per cent, although it must be noted that such figures refer as a rule only to the incidence of mastitis while the patient was in the hospital. Older writers, however, such as von Winckel, in 1878, gave 5.9 per cent and Kohler, in 1882, cited 13 per cent. It is probable that the sanitary conditions under which the women of this report bore their children more nearly approximate those on which the older figures are based.

In passing, it is interesting to note that in spite of the general fall in the apparent incidence of puerperal mastitis since von Winckel's day and the improved hygiene of the lactating breast in civilized countries, there has been no evident corresponding fall in the frequency of mammary cancer.

A division of the types of mastitis in the history adds a little more hope of accuracy.

(1) Nonsuppurative Mastitis: The apparent occurrence of this disease almost exclusively in the breast affected by the later developing tumor (table 4) is in agreement with the results of Lane-Claypon's studies and gives perhaps some special significance to this feature of the histories. Yet certain reservations must be made. 1. The determination from the history of what should be listed as nonsuppurative mastitis and what engorgement is nearly impossible. It is therefore small wonder that the estimates on the occurrence of mastitis in the history of breast cases have varied from 5.3 to 89 per cent (Lane-Claypon). 2. The localization by the patient of the side in which the mastitis occurred is extremely susceptible to suggestive influences. 3. The fact that nonsuppurative mastitis was a trifle more frequent in the benign than in the malignant series alone detracts from the weight of the evidence, if there be any, that it is in any way related to cancer apart from tumors in general.

(2) Suppurative Mastitis: In abscess of the breast one has a definitely determinable subject for historical study since all patients remember an incision. The incidence of abscess of the breast in the history of the women in this study (2.4 per cent of the lactations of the benign series and 3.4 per cent of the malignant series) is apparently somewhat higher than the averages reported by most modern hospitals (Baer and Reis), but as has been noted such reports deal only with women under the most careful supervision and include only the abscesses

TABLE 4.—*Lactation Accidents*

Engorgement Per Cent Based on Total Women Mastitis and Abscess Per Cent Based on Total Births	Premenopause						Menopause						Postmenopause						Total					
	Women	Births	Engorgement		Mastitis		Abscess		Women	Births	Engorgement		Mastitis		Abscess		Women	Births	Engorgement		Mastitis		Abscess		Women	Births	Engorgement		Mastitis		Abscess	
			No.	%	No.	%	No.	%			No.	%	No.	%	No.	%			No.	%	No.	%	No.	%			No.	%	No.	%	No.	%
Fibro-adenomas	5	9	3	60	1	11.0	0	0	2	4	1	50	1	25.0	0	0	1	7	0	0	0	0	0	0	8	20	4	50	2	10.0	0	0
Painful nodules	10	13	4	40	1	7.7	0	0	0	0	0	..	0	0	0	0	0	...	..	..	..	0	..	...	10	13	4	40	1	8.0	0	0
Chronic mastitis	23	51	11	48	4	8.0	1	2.0	18	60	8	44	0	0	3	5.0	2	4	1	50	0	0	0	0	43	115	20	46	4	3.5	4	3.5
Papillary tumors	4	8	4	100	2	25	0	0	2	6	0	0	0	0	0	0	1	1	0	0	0	0	0	0	7	15	4	57	2	13.0	0	0
Total benign	42	81	22	52	8	10.0	1	1.2	22	70	9	41	1	1.4	3	4.3	4	12	1	25	0	0	0	0	68	163	32	47	9	5.5	4	2.4
Malignant	28	66	13	46	2	3.0	5	7.5	50	146	17	34	5	3.4	3	2.0	35	137	13	37	6	4.4	4	3.0	113	349	43	38	13	3.7	12	3.4

Summary on breast affected.—Mastitis: benign; tumor side, 8; bilateral, 1; normal, 1, 0.; malignant; tumor side, 10; bilateral, 0; normal, 3.
Abscess: Benign; tumor side, 3; bilateral, 0; normal, 1; malignant; tumor side, 7; bilateral, 1; normal, 4.

of the early puerperium. It appears then that the incidence of abscess of the breast among cases of tumor was slightly if at all above that of the general frequency. This result agrees with Lane-Claypon's conclusions on her larger series.

It should be noted furthermore that of the seven patients with cancer who had a history of abscess in the same breast, three showed the scar in a different quadrant from that of the tumor, two showed no scar and in a sixth a small lump from which the cancer was said to have arisen had preceded the abscess by many years.

(*C*) *Abscess Unrelated to Pregnancy* (table 5).—Six patients, three with benign and three with malignant growths, gave histories of an abscess of the breast when not pregnant. This is a very high incidence.

TABLE 5.—*Previous Nonpuerperal Breast Disease* *

	Premenopause		Menopause		Postmenopause		Total	
	Abscess	Previous Tumor	Abscess	Previous Tumor	Abscess	Previous Tumor	Abscess	Previous Tumor
Fibro-adenoma	0	3	0	0	0	1	0	4
Painful nodule	0	1	0	0	0	0	0	1
Chronic mastitis	3	1	0	3	0	2	3	6
Papillary growths	0	0	0	0	0	1	0	1
Benign	3	5	0	3	0	4	3	12
Malignant	1	2	2	2	0	4	3	8

* Of six nonpuerperal abscesses, four were on normal side, one on tumor side and one undetermined.

Previous tumors includes those removed and also certain long existent quiescent lumps out of which a malignant growth appears to have originated.

It is not clear whether these abscesses should be regarded as significant from their possible character as inflammations, perhaps tuberculous, or as infected cystic tumors. The majority were in the breast unaffected by the later tumors.

(*D*) *Previous Tumors of the Breast* (table 5).—The history of the existence of other tumors prior to the one for which the patient entered the hospital adds considerable to the complexities of localizing the time at which one should seek for the etiologic factor. In table 5 are given the combined figures of the patients from whom a tumor of the breast had been previously removed and those in whom the present malignant growth appeared to have originated from a long existent benign one. Table 7 shows that many of these growths had been present for a long time.

It is noteworthy that the highest frequency of a history of such previous tumors was in the old age group, an observation which to a small degree supports the suggestion that the old age tumors are malignant transformations of benign abnormal tissue the etiologic basis of which lies back during the period of ovarian activity.

TABLE 6.—*Incidence of Trauma*

	Premenopause					Menopause					Postmenopause					Total				
	Total Cases	Per Cent with Trauma	Definite	Vague	Chronic	Total Cases	Per Cent with Trauma	Definite	Vague	Chronic	Total Cases	Per Cent with Trauma	Definite	Vague	Chronic	Total Cases	Per Cent with Trauma	Definite	Vague	Chronic
Fibro-adenoma	21	33	2	5	0	4	(25)	0	1	0	1	0	0	0	0	26	32	2	6	0
Painful nodules	21	38	2	5	1	1	0	0	0	0	0	.....	..	..	..	22	36	2	5	1
Chronic mastitis	30	30	2	6	1	24	0	0	0	0	3	(33)	0	1	0	57	17	2	7	1
Papillary tumors	5	20	0	1	0	4	0	0	0	0	1	(100)	1	0	0	10	20	1	1	0
Total benign	77	32	6	17	2	33	3	0	1	0	5	(40)	1	1	0	115	24	7	19	2
Malignant	41	36	6	9	0	65	25	4	10	2	49	39	6	5	8	155	32	16	24	10

Explanation.—Definite trauma: single injury to breast with tumor. Vague trauma: localization and time of injury in doubt. Chronic trauma: repeated slight injury as with a crutch or from corset steels.

(*E*) *Previous Breast Trauma* (table 6).—The possibility that trauma may be capable of initiating abnormal epithelial proliferation in the breast is testified to by certain histologic studies such as those of Bartlett who has reported seven cases of unilateral hypertrophy of the breast before puberty and one in a man over 70, all following an injury. That these breasts, though unilaterally developed, were themselves more or less symmetrically formed makes it appear probable that the trauma was only one of the causes of the growth.

Lane-Claypon's review points out that a history of breast trauma has been found in cases of cancer in from 2.6 to 44.6 per cent, depending on the observer, and it is quite likely that in any series a persistent questioner could run the figure to nearly 100 per cent. Lane-Claypon's

TABLE 7.—*Elapsed Time Since Occurrence of Trauma and Appearance of Previous Tumor*

	Benign											Malignant										
	Time Unknown	Less Than 1 Mo.	1 Mo.-6 Mos.	7 Mos.-12 Mos.	1 Yr.-2 Yrs.	3 Yrs.-5 Yrs.	6-10 Years	11-20 Years	21-30 Years	Over 30 Yrs.	Totals	Time Unknown	Less Than 1 Mo.	1 Mo.-6 Mos.	7 Mos.-12 Mos.	1 Yr.-2 Yrs.	3 Yrs.-5 Yrs.	6-10 Years	11-20 Years	21-30 Years	Over 30 Yrs.	Totals
Definite trauma	0	2	2	0	1	0	1	1	0	0	7	0	2	1	4	4	1	2	1	0	1	16
Vague trauma	2	3	3	5	3	2	0	1	0	0	19	8	4	4	1	2	5	0	0	0	0	24
Chronic trauma	1	0	0	0	0	0	0	1	0	0	2	10	0	0	0	0	0	0	0	0	0	10
Previous tumors	0	0	0	0	1	1	2	4	1	3	12	0	0	0	0	0	2	3	0	0	3	8

very careful study of this question in which the cases were separated into those with and those without actual bruising of the skin appeared to indicate rather definitely that traumatism played a part in the production of cancer.

The distribution of a history of trauma among the different tumor groups of the present series is presented in table 6. The equal incidence of trauma in cases of carcinoma, fibro-adenoma and "painful nodule," as compared with the much lower incidence in the cases of diffuse chronic mastitis, implies that the presence of a lump may well have the suggestive effect attributed to it, for few authors would ascribe much importance to trauma as a factor in the production of fibro-adenomas. The age distribution of the frequency of trauma shows a strange drop in the group of women who developed cancer near the menopause. The factor of chronic trauma appears chiefly in the oldest group, possibly because women of this age and generation are wearing corsets, but perhaps because in the older women an extrinsic factor is required to start growth.

In general, it must be said, as Dietrich and Frangenheim have pointed out, that if trauma is a factor it is surprising that cancer of the breast is not much more common among the industrial and peasant working classes and much less common among the well to do.

ABNORMALITIES OF OVARIAN FUNCTION

The possibilities for the studies of an organ's function afforded in the ovary by the phenomenon of menstruation are in a sense unique, for the effect of what may often be minor variations in organic structure, appear at once in the form of definite variations in the interval, duration and amount of menstrual flow. Such symptoms are readily translatable into quantitative data by the patient herself and since the constant repetition of the menstrual phenomenon has given her training on the subject and because the necessities of hygiene force the occurrence of changes in type on her consciousness, the testimony of the patient on this subject gives information more accurate than most data similarly obtained.

The majority of the few writers who have sought for it have failed to find a clinical ground for believing that abnormalities of menstruation are in any way connected with cancer of the breast. Simons, although he reported several cases of atypical menses in younger women with carcinoma of the breast, comes to no conclusions in regard to the etiologic relation of menstruation to cancer. Lane-Claypon also reported almost completely negative results, although she stated as her opinion that there may none the less be some relation between menstruation and tumor growth in the breast.

In the present study, the ovarian activity will be analyzed from several angles, based on the following suppositions: 1. The original or characteristic type of menstruation which the patient experienced in her early years of maturity is an index of her normal ovarian constitution. 2. The "present type," namely, that which the patient is experiencing at the time of the tumor's onset is the product of the original constitution and the modifying influences of acquired pelvic disease and the degenerative changes of age. It is in general the more significant of the two since it is under its régime that the tumor has theoretically taken origin. 3. Changes in the type of menstruation indicate a change in the effect of the ovarian secretion on the endometrium and hence probably also on the breast. 4. The character of certain other processes such as puberty and the menopause as well as the symptoms of premenstrual pain and dysmenorrhea give varying indications of the constitution and condition of the reproductory system.

(*A*) *Puberty; The Onset of Menstruation.*—Abnormalities of puberty, particularly that of late onset, have been shown to be fre-

quently indicative of genital underdevelopment (Rossi Doria) and have been found with special frequency in the history of women with certain types of new growth, notably carcinoma of the fundus (Mayer).

The average age of puberty in these women with tumors of the breast is shown in table 8 to be approximately 14 years, which corresponds almost exactly with the normal for American girls as determined by Engelmann, although it is somewhat lower than the average age for the European countries in which many of the women were born (Schaeffer, Schröder). If, however, one regards as slightly abnormal a puberty that occurs before the thirteenth or after the sixteenth year, one finds such deviations from the normal slightly more often among patients with fibro-adenoma and among young patients with cancer than in the other tumor groups.

(*B*) *The Periodicity of Menstruation.*—The chronologic rhythm of the menstrual flow supplies a pure index of ovarian function, for the time of the periods is determined entirely by ovulation. According to Schröder, a short cycle is to be explained on the basis of an early death of the ovum and as such is probably not productive of permanent hyperplastic changes in the epithelium of the breast unless a too rapid recurrence of the stimulative phase could produce such effects. A long interval may on the other hand be the result of a persistent follicle the supposed cause of hyperplastic endometritis or the result of a persistent corpus luteum which has also been reported as the cause of a marked degree of endometrial hypertrophy (Curtis). To link these facts to those of the pathology of the breast there is the similarity between the causes of physiologic activity in breast and endometrium and also certain histologic evidence offered by Dieckmann's observation of pathologic proliferation in the breasts of women suffering from amenorrhea of long standing.

A brief explanation of the methods used in compiling tables 9 *A* and *B* is necessary. The types of period were classed as four week periods if the cycle was of not less than twenty-six or more than thirty-one days and also if greater deviations were of only occasional occurrence. Thus the group regarded as normal contains some women with minor irregularities and the groups of women reported as having periods recurring at three to four or four to five week intervals comprises only cases with definite deviations from the normal. The groups listed under three weeks and under five weeks include also some women who were menstruating every two weeks and some every six to twelve weeks, respectively.

Although the chief conclusions are to be drawn from the comparison of relative incidence of menstrual irregularities in the various pathologic and age groups of this series, it is perhaps useful for the purpose

TABLE 8.—*Age of Puberty*

	Premenopause					Menopause					Postmenopause					Total				
	Total Cases	Average Age	% Normal	% Early	% Late	Total Cases	Average Age	% Normal	% Early	% Late	Total Cases	Average Age	% Normal	% Early	% Late	Total Cases	Average Age	% Normal	% Early	% Late
Fibro-adenoma	20	13.5	45	35	20	3	(15.5)	(33)	0	(67)	1	(18.0)	0	0	(100)	24	14.0	42	29	29
Painful nodules	18	14.0	83	11	6	1	(14.0)	(100)	0	0	0	.....	.....	..	.....	19	14.0	84	11	5
Chronic mastitis	23	13.5	83	8	8	21	14.0	57	14	29	3	(14.5)	(100)	0	0	47	14.0	72	11	17
Papillary growths	5	(15.0)	(20)	(20)	(60)	3	(15.5)	(33)	0	(67)	1	(13.0)	(100)	0	0	9	15.0	11	33	55
Total benign	66	13.8	67	19	13	28	14.5	53	11	36	5	14.8	(80)	0	(20)	99	14.1	64	15	21
Total malignant	34	14.0	62	23	15	57	14.0	60	19	21	45	14.2	60	20	20	136	14.1	60	21	19

Explanation.—Normal puberty at 13, 14 or 15 years.

of general orientation to note that from the examination of the statistics of several writers (Krieger, Kelly, Hart and Barbour, Webster), it appears that a minimum of 75 per cent of all women have a twenty-six to thirty day cycle, while some writers have placed the figure as high as 95 per cent.

The tables dealing with menstrual frequency (9 *A* and *B*) contain material which in its implications is the most important in the paper. A few special points must be made.

1. The original or "constitutional" pattern of menstruation is perhaps as often normal among women with chronic mastitis and with carcinoma at all ages as it is for women in general, but a larger percentage of the women with fibro-adenomas and "painful nodules" have suffered from irregular types of menstruation since puberty (table 9 *A*).

2. The frequency of original abnormalities shows a steady decrease with the increase in the age of tumor incidence, which is perhaps due to the displacement of congenital anomalies as exciting agents by other forms of ovarian disorder.

3. Turning to a consideration of the type of menstruation being experienced by the patients at the time of the onset of the tumor, one finds a great increase in the percentage of women with abnormal periodicity. This increase affects practically all of the pathologic groups and it is striking that the occurrence of these irregular types is almost as common in the young women as it is in those over 40 in whom a greater frequency should be looked for on account of the nearness of the menopause.

4. It is possibly significant that among the major types of menstrual anomaly, it is particularly the increased interval variety that shows the gain. This tendency toward a longer cycle is particularly marked among the malignant cases.

5. Of the women who were still menstruating when the tumor appeared, 33 per cent with benign and 32 per cent with malignant growths had experienced an alteration in the length of the interval (table 11 *A*). That most of the new types of menstruation have appeared within a short time before the appearance of the breast tumor is shown in table 12.

(*C*) *The Volume and Duration of Menstruation.*—The number of days of flow and the quantity of blood lost bear a less direct relationship to the ovarian function than does the periodicity just discussed. Particularly is increased duration or strength of flow rarely a true measure of ovarian function but is more indicative of a local pathologic process in the pelvis such as inflammations, congestions, tumors and displacements. Diminished bleeding, on the other hand, may as a rule be regarded as a sign of ovarian insufficiency. These principles are to be applied in the interpretation of tables 10 *A* and *B*.

TABLE 9.—*A. Original Types of Menstrual Cycle*

	Premenopause							Menopause							Postmenopause							Totals						
	Available Cases	Total, 4 Weeks	Per Cent, 4 Weeks	3 Weeks or Less	5 Weeks or More	3-4 Weeks	4-5 Weeks	Available Cases	Total, 4 Weeks	Per Cent, 4 Weeks	3 Weeks or Less	5 Weeks or More	3-4 Weeks	4-5 Weeks	Available Cases	Total, 4 Weeks	Per Cent, 4 Weeks	3 Weeks or Less	5 Weeks or More	3-4 Weeks	4-5 Weeks	Available Cases	Total, 4 Weeks	Per Cent, 4 Weeks	3 Weeks or Less	5 Weeks or More	3-4 Weeks	4-5 Weeks
Fibro-adenomas	21	12	57	3	3	3	0	4	2	50	0	0	2	0	1	1	(100)	0	0	0	0	26	15	58	3	3	5	0
Painful nodules	21	10	48	1	3	6	1	1	0	0	0	0	0	1	0	..	.....	..	..	..	..	22	10	45	1	3	6	0
Chronic mastitis	30	25	83	0	2	3	0	24	19	79	2	2	1	0	0	..	.....	..	..	..	..	57	47	83	2	4	4	0
Papillary growths	6	2	33	2	1	1	0	4	3	75	0	0	1	0	1	1	(100)	0	0	0	0	11	6	55	2	1	2	0
Total benign	78	49	63	6	9	13	1	33	24	73	2	2	4	1	5	5	(100)	0	0	0	0	116	78	67	8	11	17	2
Malignant	41	31	76	3	1	5	1	65	59	91	4	0	2	0	49	48	97	1	0	0	0	155	138	89	8	1	7	1

B. Types of Menstrual Cycle at Time of Onset of Tumor

	Premenopause							Menopause (Exclusive of B_3)							Totals						
	Available Cases	Total, 4 Weeks	Per Cent, 4 Weeks	3 Weeks or Less	5 Weeks or More	3-4 Weeks	4-5 Weeks	Available Cases	Total, 4 Weeks	Per Cent, 4 Weeks	3 Weeks or Less	5 Weeks or More	3-4 Weeks	4-5 Weeks	Available Cases	Total, 4 Weeks	Per Cent, 4 Weeks	3 Weeks or Less	5 Weeks or More	3-4 Weeks	4-5 Weeks
Fibro-adenomas	21	11	52	1	3	3	3	1	(33)	1	0	1	0	24	12	50	4	1	4	3
Painful nodules	21	8	38	3	4	5	1	1	0	0	0	1	0	22	8	37	3	4	6	1
Chronic mastitis	30	19	63	2	1	7	1	20	11	55	2	4	3	0	49	30	61	4	5	10	0
Papillary growths	6	1	17	3	1	1	0	3	1	(33)	0	1	0	1	9	2	22	3	2	1	1
Total benign	78	39	50	11	7	16	5	27	13	48	3	5	5	1	104	52	50	14	12	21	5
Malignant	41	23	56	5	6	5	2	43	22	49	3	14	3	1	84	45	54	8	20	8	3

Since the amount and the duration of flow bear almost the same significance and since the patient's reports of amounts are difficult to analyze, the study will be limited to the question of the number of days of flow except in the consideration of changes in menstruation when the patient's report of changes in volume (as opposed to actual volume) appears to be reliable.

As regards the usual monthly duration of menstruation, it may be said that any length of flow within the range of from three to six days cannot be considered abnormal. In 500 cases in private practice, Bland reported that 77.8 per cent of the women had periods lasting from three to six days, 15.4 per cent for a longer and 6.8 per cent for a shorter time. In 4,542 cases, Mayer found 6 per cent with from one to two day periods and 28.8 per cent with from seven to eight day periods.

From a study of table 10 *B*, the following is to be noted:

1. The original duration of the menses is practically the same in each tumor group as it is for women in general.

2. When the duration of the menses as present at the time of onset of the tumor is studied (table 10 *B*), it is found that there is a small but definite increase in the percentage of cases with an abnormally short flow. This frequency of a short type of menstruation is found most often in relation to cases of carcinoma and of chronic mastitis. Particularly in the group of malignant tumors it is noticeable that a decrease in the amount or duration of bleeding is found almost as often in the young group of women as it is in those of the menopausal ages.

3. In regard to the changes in amount or duration of the menses of the individual patients (table 11 *B*), it is found that such changes had occurred in 46 per cent of all benign and 41 per cent of all malignant cases. These changes were usually of the nature of a decrease in amount and duration of flow. That most of these changes occurred in close proximity to the time of the incidence of the tumor is shown in table 12.

Summary.—A study of the subject of a menstrual change of some type, i. e., either of frequency, duration or volume of menses or any combination of these, as outlined in table 11 *C*, indicates that well over a half of the women, who were still menstruating at the time of the onset of the tumor, had noted a recent change in the characteristics of their menstruation indicating some minor or major variation in the ovarian effect on the endometrium. Yet an empirically determined association of menstrual irregularities might perhaps have little claim to serious consideration, were there not reasons for believing that certain of these changes might be expected to produce proliferative processes in the breast.

TABLE 10.—*A. Original Duration of Menstrual Periods*

	Premenopause							Menopause							Postmenopause							Total						
	Available Cases	Total 3-6 Days	Per Cent 3-6 Days	1-2 Days	3-4 Days	5-6 Days	7 Days and Over	Available Cases	Total 3-6 Days	Per Cent 3-6 Days	1-2 Days	3-4 Days	5-6 Days	7 Days and Over	Available Cases	Total 3-6 Days	Per Cent 3-6 Days	1-2 Days	3-4 Days	5-6 Days	7 Days and Over	Available Cases	Total 3-6 Days	Per Cent 3-6 Days	1-2 Days	3-4 Days	5-6 Days	7 Days and Over
Fibro-adenomas	21	17	81	1	8	9	3	4	3	(75)	0	2	1	1	1	1	(100)	0	1	0	0	26	21	81	1	11	10	4
Painful nodules	21	18	85	1	9	9	2	1	1	(100)	0	1	0	0	0	..	.....	..	..	..	..	22	19	86	1	10	9	2
Chronic mastitis	30	28	93	1	18	10	1	24	18	75	3	13	5	3	3	3	(100)	0	2	1	0	57	49	86	4	33	16	4
Papillary growths	6	4	67	0	1	3	2	4	4	(100)	0	3	1	0	1	1	(100)	0	1	0	0	11	9	82	0	5	4	2
Total benign	78	67	86	3	36	31	8	33	26	80	3	19	7	4	5	5	(100)	0	4	1	0	116	98	84	6	59	39	12
Malignant	41	33	80	5	23	10	3	64	48	75	4	32	16	12	49	41	84	4	28	13	4	154	122	79	13	83	39	19

B. Duration of Menstrual Periods at Time of Onset of Tumor

	Premenopause							Menopause (Exclusive of B_3)							Total						
	Available Cases	Total 3-6 Days	Per Cent 3-6 Days	1-2 Days	3-4 Days	5-6 Days	7 Days and Over	Available Cases	Total 3-6 Days	Per Cent 3-6 Days	1-2 Days	3-4 Days	5-6 Days	7 Days and Over	Available Cases	Total 3-6 Days	Per Cent 3-6 Days	1-2 Days	3-4 Days	5-6 Days	7 Days and Over
Fibro-adenomas	21	16	76	2	7	9	3	3	3	(100)	0	1	2	0	24	19	80	2	8	11	3
Painful nodules	21	17	81	2	11	6	2	1	1	(100)	0	1	0	0	22	18	82	2	12	6	2
Chronic mastitis	30	24	80	6	15	9	0	19	11	57	4	7	4	4	49	35	71	10	22	13	4
Papillary tumors	6	3	50	1	0	3	2	3	3	(100)	0	0	3	0	9	6	67	1	0	6	2
Total benign	78	60	77	11	33	27	7	26	18	69	4	9	9	4	104	78	75	15	42	36	11
Malignant	38	28	74	8	21	7	2	40	25	63	7	16	9	8	78	53	68	15	37	16	10

TABLE 11.—*A. Changes in Periodicity of Menstruation*

	Premenopause					Menopause (Exclusive of B_3)					Totals				
	Available Cases	Total With Change in Periodicity	Per Cent With Change in Periodicity	Increased Frequency (Shorter Cycles)	Decreased Frequency (Longer Cycles)	Available Cases	Total With Change in Periodicity	Per Cent With Change in Periodicity	Increased Frequency	Decreased Frequency	Available Cases	Total With Change in Periodicity	Per Cent With Change in Periodicity	Increased Frequency	Decreased Frequency
Fibro-adenomas	21	3	14	1	2	3	0	0	0	0	24	3	12	1	2
Painful nodules	21	8	38	5	3	1	1	(100)	0	1	22	9	41	5	4
Chronic mastitis	30	9	30	7	2	20	10	50	7	3	50	19	38	14	5
Papillary tumors	6	3	50	3	0	3	1	(33)	0	1	9	4	44	3	1
Total benign	78	23	31	16	7	27	12	44	7	5	105	35	33	23	12
Malignant	41	10	24	4	6	43	17	40	4	13	84	27	32	8	19

B. Changes in Volume and Duration of Menstruation

	Premenopause									Menopause (Exclusive of B_3)										Totals								
				Duration			Volume						Duration			Volume						Duration			Volume			
	Available Cases	Total Change in Volume or Duration	Per Cent With Change in Volume or Duration	Increase	Decrease	Total	Increase	Decrease	Total	Available Cases	Total Change in Volume or Duration	Per Cent With Change in Volume or Duration	Increase	Decrease	Total	Increase	Decrease	Total	Available Cases	Total Change in Volume or Duration	Per Cent With Change in Volume or Duration	Increase	Decrease	Total	Increase	Decrease	Total
Fibro-adenomas	21	3	14	0	1	1	1	2	3	3	1	33	0	1	1	0	1	1	24	4	17	0	2	2	1	3	4
Painful nodules	21	9	43	2	6	8	1	4	5	1	1	100	0	1	1	0	1	1	22	10	45	2	7	9	1	5	6
Chronic mastitis	30	13	43	2	6	8	3	8	11	20	17	85	6	7	13	8	5	13	50	30	60	8	13	21	11	13	24
Papillary tumors	6	2	33	0	1	1	1	1	2	3	2	67	0	1	1	0	2	2	9	4	44	0	2	2	1	3	4
Total benign	78	27	35	4	14	18	6	15	21	27	21	67	6	10	16	8	9	17	105	48	46	10	24	34	14	24	38
Malignant	41	15	37	1	9	10	1	12	13	43	19	44	4	9	13	3	15	18	84	34	41	5	18	23	4	27	31

(*D*) *Dysmenorrhea.*—Dysmenorrhea in the present study refers only to the primary type which is nearly always evidence of a minor anatomic malformation (Joachimovits). It is from the point of view of this associated underdevelopment that this symptom is being studied. An approximate idea of the general frequency of dysmenorrhea may be obtained from recent studies of Sturgis and van Duyne which indicate that from 0.3 to 7 per cent of women have severe pain and from 15 to 30 per cent moderate discomfort at their periods.

TABLE 11 *C.—Change in Menstruation of Some Type*

	Puberty to 35, A_1			35 to 40, A_2			40 to Menopause, B_1			Menopause, B_2			Total		
	Available Cases	Cases With Menstrual Change	Per Cent With Change	Available Cases	Cases With Menstrual Change	Per Cent With Change	Available Cases	Cases With Menstrual Change	Per Cent With Change	Available Cases	Cases With Menstrual Change	Per Cent With Change	Available Cases	Cases With Menstrual Change	Per Cent With Change
Fibro-adenomas	18	4	22	3	2	(66)	2	0	0	1	1	100	24	7	29
Painful nodules	20	10	50	1	1	(100)	0	..	..	1	1	100	22	12	54
Chronic mastitis	22	13	59	8	5	(63)	3	0	0	17	17	100	50	35	70
Papillary tumors	2	0	0	4	4	(100)	0	..	..	3	3	100	9	7	78
Total benign	62	27	44	16	12	75	5	0	0	22	22	100	105	61	58
Malignant	17	9	53	24	9	38	18	0	0	25	25	100	84	43	51

TABLE 12.—*Elapsed Time Between Alteration in Menses and Onset of Tumor*

	Benign					Malignant				
	Exact Time Not Stated	0-23 Months	2-4½ Years	5-10 Years	Total	Exact Time Not Stated	0-23 Months	2-4½ Years	5-10 Years	Total
Periodicity Change	3	18	9	5	35	0	21	3	3	27
Duration Change	1	22	7	4	34	2	14	2	4	22
Volume Change	2	23	9	4	38	2	21	4	4	31

Note.—To the women of table 12, there could be added the women of class B_2 (benign, 6, malignant, 22) who had had the changes of the menopause from six months to five years before the apparent onset of the tumor, and the women of C_1 (benign, 3; malignant, 24) who had had these changes from five to ten years previously.

In table 13 *A*, showing original frequency of dysmenorrhea and by implication the frequency of moderate maldevelopment, it is clear that the fibro-adenomas again depart markedly from the average while the other groups except for the carcinomas of the early years do not vary from the ranges of van Duyne and Sturgis. Table 13 *B*, illustrating the frequency of dysmenorrhea at the time of onset of the tumor, shows that the supposed maldevelopment has to a considerable extent disappeared in the cases of early malignancy but has persisted for the fibro-adenomas. The fact that the majority of the women with fibro-

TABLE 13.—*A. Incidence of Dysmenorrhea During Early Life*

	Premenopause					Menopause					Postmenopause					Totals				
	Available Cases	Women without Pain	Per Cent Without Pain	Moderate Pain	Severe Pain	Available Cases	Women without Pain	Per Cent Without Pain	Moderate Pain	Severe Pain	Available Cases	Women without Pain	Per Cent Without Pain	Moderate Pain	Severe Pain	Available Cases	Women without Pain	Per Cent Without Pain	Moderate Pain	Severe Pain
Fibro-adenomas	21	7	33	5	9	4	1	(25)	2	1	1	1	(100)	0	0	26	9	35	7	10
Painful nodules	21	11	52	5	5	1	1	(100)	0	0	0	0	.....	0	0	22	12	54	5	5
Chronic mastitis	30	21	70	7	2	24	15	63	7	2	3	2	(67)	0	1	57	38	67	14	5
Papillary tumors	6	2	30	3	1	4	2	(50)	2	0	1	0	0	0	1	11	4	36	5	2
Total benign	78	41	53	20	17	33	19	58	11	3	5	3	(60)	0	2	116	63	54	31	22
Malignant	40	15	38	17	8	64	38	59	20	6	49	28	57	18	3	153	81	53	55	17

B. Incidence of Dysmenorrhea at Time of Onset of Tumor

	Premenopause					Menopause					Totals				
	Available Cases	Women without Pain	Per Cent Without Pain	Moderate Pain	Severe Pain	Available Cases	Women without Pain	Per Cent Without Pain	Moderate Pain	Severe Pain	Available Cases	Women without Pain	Per Cent Without Pain	Moderate Pain	Severe Pain
Fibro-adenomas	21	6	28	7	8	3	1	(33)	1	1	24	7	29	8	9
Painful nodules	21	12	57	6	3	1	1	(100)	0	0	22	13	59	6	3
Chronic mastitis	30	18	60	9	3	20	14	70	5	1	50	32	64	14	4
Papillary tumors	6	3	50	2	1	3	3	(100)	0	0	9	6	66	2	1
Total benign	78	39	50	24	15	27	19	70	6	2	105	58	55	30	17
Malignant	39	22	56	14	3	42	28	67	12	2	81	50	62	26	5

adenomas suffered not only pain but severe pain is corroborative evidence that fibro-adenomas occur chiefly in relatively undeveloped women.

(*E*) *Premenstrual Breast Symptoms.*—The significance of premenstrual pain and swelling in relation to hyperplasia of the epithelium and the association of these symptoms with pelvic disorders have been discussed. As the characteristics of these painful breast symptoms are not very well known, however, the following case history is cited as a fair though perhaps unusually clearcut example:

R. F., aged 31, was married six and a half years before examination and widowed four years before. During her only pregnancy, which ended in a miscarriage at three and a half months, she suffered from excessive vomiting and severe breast pain. The menses had been regular since marriage but irregular previously. Eight months before admission the patient received an injury in the left breast which caused a small red spot. Six weeks later, having had in the meantime no breast symptoms, she was seized with a severe attack of nausea and vomiting, and her left breast became diffusely enlarged and tender. She was confined in bed for a week. During succeeding months the breast improved but was still tender, especially in the premenstruum. The opposite breast also became somewhat painful. Examination revealed a slender, nervous, weeping, blonde woman. Both breasts were medium-sized but erect, with firm nodular centers and normal nipples and areolae. In the outer upper quadrant of the left breast there was an ill defined lump 6 cm. in diameter, exquisitely tender. The right breast was similar, a trifle smaller and also with a tender lumpiness in the outer part. The thyroid was definitely enlarged. Pelvic examination disclosed a small, conical cervix, a small, anteflexed uterus tipped to the left and an enlarged, slightly tender, probably "cystic" left ovary. During two months of observation the patient has improved somewhat under a prescription of corpus luteum taken during ten days preceding menstruation and with the use of a breast support.

The study of menstrual breast symptoms (tables 14 *A* and *B*) reveals that a certain number of women, particularly those in whom tumors developed at an early age, had suffered from breast pain before their periods since puberty. For many of the women, however, these premenstrual symptoms were of recent origin (table 15 *A*), a fact rather surprising since increasing age and marriage appear as a rule to alleviate these complaints. The close relation between the time of onset of these symptoms and the discovery of the tumor is of great importance if one accepts the view that breast pain before the periods is dependent on excessive corpus luteum stimulation.

(*F*) *Theoretical Anomalies of Pregnancy and Lactation.*—Beside the irregular ovarian activity discussed under menstruation, there must also be considered the possibility of abnormal stimuli to the breast during gestation and lactation.

The occurrence of cancer of the breast of a peculiarly malignant variety is often observed during pregnancy. That the pregnancy is actually an important factor in initiating growth is indicated by the

TABLE 14.—*A. Incidence of Premenstrual Breast Symptoms in Early Life*

	Premenopause					Menopause					Postmenopause					Totals				
	Available Cases	Women Without Breast Symptoms	Per Cent Without Breast Symptoms	Women With Pain	Women With Swelling	Available Cases	Women Without Breast Symptoms	Per Cent Without Breast Symptoms	Women With Pain	Women With Swelling	Available Cases	Women Without Breast Symptoms	Per Cent Without Breast Symptoms	Women With Pain	Women With Swelling	Available Cases	Women Without Breast Symptoms	Per Cent Without Breast Symptoms	Women With Pain	Women With Swelling
Fibro-adenomas	21	9	43	9	9	4	3	(75)	1	1	1	1	(100)	0	0	26	13	50	10	10
Painful nodules	21	13	62	8	6	1	1	(100)	0	0	0	0	.....	..	..	22	14	64	8	6
Chronic mastitis	30	13	43	9	13	24	18	75	5	1	3	3	(100)	0	0	57	34	60	14	14
Papillary tumors	6	3	50	2	2	4	4	(100)	0	0	1	1	(100)	0	0	11	8	73	2	2
Total benign	78	38	49	28	30	33	26	79	6	2	5	5	100	0	0	116	69	60	34	32
Malignant	41	19	46	15	14	65	41	63	16	16	49	44	89	4	2	155	104	67	35	32

B. Incidence of Premenstrual Breast Symptoms at Time of Onset of Tumor

	Premenopause					Menopause					Totals				
	Available Cases	Women Without Breast Symptoms	Per Cent Without Breast Symptoms	Women With Pain	Women With Swelling	Available Cases	Women Without Breast Symptoms	Per Cent Without Breast Symptoms	Women With Pain	Women With Swelling	Available Cases	Women Without Breast Symptoms	Per Cent Without Breast Symptoms	Women With Pain	Women With Swelling
Fibro-adenomas	21	7	33	11	10	3	2	(67)	1	1	24	9	38	12	11
Painful nodules	21	0	0	21	14	1	0	0	1	1	22	0	0	22	15
Chronic mastitis	30	13	43	13	13	20	14	70	3	4	50	27	54	16	17
Papillary tumors	6	1	17	4	2	3	3	(100)	0	0	9	4	44	4	2
Total benign	78	21	27	49	39	27	19	70	5	6	105	40	38	54	45
Malignant	39	18	46	13	11	43	25	58	13	11	82	43	52	26	22

reports of development of cancer during gestation in a single breast after the previous removal of the other for carcinoma. Trout observed this happening in the later history of two of his own cases and in reply to his inquiries sent to other physicians learned of thirteen similar instances.

Development of cancer during lactation may be attributable to the increase in size of microscopic cancer seeds formed during the

TABLE 15.—*A. Changes in Severity of Dysmenorrhea and Breast Symptoms Before Onset of Tumor*

	Premenopause						Menopause Exclusive of B_3						Totals					
	Dysmenorrhea			Breast Symptoms			Dysmenorrhea			Breast Symptoms			Dysmenorrhea			Breast Symptoms		
	Available Cases	Increase	Decrease	Available Cases	Increase	Decrease	Available Cases	Increase	Decrease	Available Cases	Increase	Decrease	Available Cases	Increase	Decrease	Available Cases	Increase	Decrease
Fibro-adenomas	21	2	2	21	2	0	3	0	0	3	0	0	24	2	2	24	2	0
Painful nodules	21	1	5	21	15	0	1	0	0	1	1	0	22	1	5	22	16	0
Chronic mastitis	30	4	1	30	12	0	20	2	3	20	3	1	50	6	4	50	15	1
Papillary tumors	6	1	1	6	2	0	3	0	1	3	0	0	9	1	2	9	2	0
Benign total	78	8	9	79	31	0	27	2	4	27	4	1	105	10	13	105	35	2
Malignant	39	0	9	39	5	4	42	1	7	43	5	1	81	1	16	82	10	5

B. Elapsed Time Between Change in Premenstrual Breast Symptoms and Onset of Tumor

	Benign						Malignant					
	Exact Time Not Noted	0-23 Months	2-4½ Years	5-10 Years	Over 10 Years	Total	Exact Time Not Noted	0-23 Months	2-4½ Years	5-10 Years	Over 10 Years	Total
Increase or new appearance	0	21	10	3	1	35	0	7	1	2	0	10
Decrease or disappearance	0	0	0	0	1	1	1	3	0	1	0	5

preceding pregnancy, but it is also possible that the irregular ovulation of the lactation period may furnish the basis for atypical cell proliferation during this time. Attempts to study the relation of the time of the return of the menses after parturition to the etiology of tumors were made on a small group of cases but no progress was made and this subject must be left in this very theoretical state.

Kilgore has reported that 4.5 per cent of all cancers of the breast arise during pregnancy or lactation and of the cancers occurring under the age of 47, 10 per cent arise under these conditions. So far as the present series of cases of cancer is concerned, the following relation to

pregnancy was noted: Of the twenty-eight women under the age of 40 who had borne children, a lump was first noted during pregnancy in two, during lactation in three, between one and two years after a delivery in three, between two and three years in one, between three and four years in three. Altogether, sixteen of the twenty-eight women (57 per cent) developed their tumor before the end of the fifth year after a delivery.

(*G*) *The Menopause.*—Lane-Claypon, by comparing the incidence of mammary cancer for any given age with the total number of women in the general population of the same age, has shown that there is probably a constant increase of susceptibility to the disease with advancing years. The proof of this relationship must end the argument about the immediate effect of the menopause on the production of cancer, yet the

TABLE 16.—*A. Average Age of Menopause*

	B_2 Menopause Incomplete		B_3 6 Months-5 Yrs. After Cessation		C_1 5-10 Years After Cessation		C_2 Over 10 Years After Cessation		Total	
	Available Cases	Average Age	Available Cases	Average Age	Available Cases	Average Age	Available Cases	Average Age	Available Cases	Average Age
Fibro-adenomas	1	48	1	42	0	....	1	42	3	44
Painful nodules	1	50	0	....	0	....	0	....	1	50
Chronic mastitis	17	45.7	4	44.5	2	46	1	51	24	45.7
Papillary tumors	3	43.7	1	50	1	52	0	....	5	47.4
Total benign	22	45.7	6	45	3	48	2	46.5	33	45.8
Malignant	25	45.4	22	48	24	47.9	25	46.6	96	46.9

Note.—It must be remembered that in group B_2, the menopause had apparently begun but was not yet completed.

possibility remains that the changes in the breast produced by the ovarian irregularities of the menopausal years may be the basis for the precancerous lesions from which cancers gradually take origin over a long period. It appears probable that the menopausal years are the last in which benign new growths and diffuse hyperplasia of the breast may originate, and so far as cancers are derivatives of these structures, the original basis of their growth must also date back to the years before the cessation of ovarian activity.

(1) The Age of the Menopause: The age at which the menopause occurs has perhaps a slight bearing on the strength of the ovarian function. Lane-Claypon's report showed that the age of menstrual cessation and the total years of sex life were essentially the same for cancer as for normal cases. In the present series (table 16 *A*), the average age of the menopause was approximately 47, which corresponds closely with the normal figures determined by several writers (Norris, 47.89; Mayer-Krieger, 47.03; Schaeffer, 47.26).

TABLE 16.—*B. Duration of Menstrual Symptoms of Menopause Before Complete Cessation*

	B_2, Tumor Onset During Existent Menopause Symptoms							B_3, 6 Months-5 Years After Cessation							C, 5 Years and Longer After Cessation							Totals						
	Available Cases	Sudden Cessation	Operative Cessation	0-6 Months	7-12 Months	13-24 Months	Over 2 Years	Available Cases	Sudden Cessation	Operative Cessation	0-6 Months	7-12 Months	13-24 Months	Over 2 Years	Available Cases	Sudden Cessation	Operative Cessation	0-6 Months	7-12 Months	13-24 Months	Over 2 Years	Available Cases	Sudden Cessation	Operative Cessation	0-6 Months	7-12 Months	13-24 Months	Over 2 Years
Fibro-adenomas	1	..	..	0	0	0	1	1	0	0	1	0	0	0	1	1	0	0	0	0	0	3	1	0	1	0	0	1
Painful nodules	1	..	..	1	0	0	0	0	..	..	..	..	..	..	0	..	..	..	..	..	..	1	0	0	1	0	0	0
Chronic mastitis	17	..	..	5	5	4	3	4	1	3	0	0	0	0	3	0	0	2	1	0	0	24	1	3	7	6	4	3
Papillary tumors	2	..	..	1	0	1	0	0	..	..	..	..	..	..	1	0	0	0	0	0	1	3	0	0	1	0	1	1
Total benign	21	..	..	7	5	5	4	5	1	3	1	0	0	0	5	1	0	2	1	0	1	31	2	3	10	6	5	5
Malignant	25	..	..	6	10	5	4	21	3	2	8	3	3	2	35	9	3	8	10	1	4	81	12	5	22	23	9	10

C. Type of Menstrual Changes Before Cessation

	B_2, Existent Menopause Symptoms								B_3, 6 Months-5 Years After Cessation								C, 5 Years and Longer After Cessation								Totals							
			Periodicity			Duration or Volume					Periodicity			Duration or Volume					Periodicity			Duration or Volume					Periodicity			Duration or Volume		
	Available Cases	Sudden Menopause (Normal or Operative)	Shorter Cycle	Longer Cycle	Per Cent Change	Increase	Decrease	Per Cent Change	Available Cases	Sudden Menopause (Normal or Operative)	Shorter Cycle	Longer Cycle	Per Cent Change	Increase	Decrease	Per Cent Change	Available Cases	Sudden Menopause (Normal or Operative)	Shorter Cycle	Longer Cycle	Per Cent Change	Increase	Decrease	Per Cent Change	Available Cases	Sudden Menopause (Normal or Operative)	Shorter Cycle	Longer Cycle	Per Cent Change	Increase	Decrease	Per Cent Change
Fibro-adenomas	1	..	0	0	..	0	1	..	1	0	0	0	..	0	1	..	1	1	0	0	..	0	0	..	3	1	0	0	..	0	2	..
Painful nodules	1	..	0	1	..	0	0	..	0	..	..	..	..	..	..	..	0	..	..	..	..	..	..	..	1	0	0	1	..	0	0	..
Chronic mastitis	17	..	6	3	..	5	7	..	4	4	0	0	..	0	0	..	3	0	0	1	..	0	3	..	24	4	6	4	..	5	10	..
Papillary tumors	3	..	1	1	..	0	2	..	1	0	0	0	..	0	1	..	1	0	0	0	..	0	1	..	5	0	1	1	..	0	4	..
Total benign	22	..	7	5	55	5	10	68	6	4	0	0	0	0	2	33	5	1	0	1	20	0	4	80	33	5	7	6	40	5	16	64
Malignant	25	..	3	14	68	7	10	68	21	5	2	12	67	3	4	33	38	12	3	18	55	6	7	34	84	17	8	44	62	16	21	44

Note: Shorter cycle is equivalent to more frequent periods.

A more important feature of the menopause than that of the age of occurrence is the character and duration of the period of irregular ovulation that precede the final cessation of menstruation. Such data could unfortunately be supplied by only a few patients.

(2) Duration of Menopause: The total time elapsing between the first irregular period and complete cessation is usually under one year. Morris reported only 13 per cent and Tilt, 28 per cent of women whose menopausal irregularities lasted over twelve months. Among the cases of tumor in this study, the duration of the menopause appears in general to be somewhat longer and this tendency is more marked in the women who developed the disease during or soon after the climax (table 16 *B*). Thus in the twenty-five cases of cancer of group B_2, menstrual irregularities had already been noted for over a year in 36 per cent, and in these it must be remembered that final cessation had not yet occurred. The cases are, of course, too few to make this observation more than suggestive.

(3) Type of Menopause: In the cases of cancer by far the commonest type of menopause was that characterized by a lengthening cycle (decreasing frequency of menstruation), 52 per cent of the women with carcinoma developing after the onset of the climax showing this feature. This form of menopause, of course, is not specific for cancer, yet it is true that an increasing interval between ovulations should theoretically be productive of irregular proliferative processes in the breast and may well be one of the causes of the minor degrees of chronic mastitis that can apparently be detected clinically in practically all breasts during the years of the menopause, and with which cancer is so commonly associated.

ASSOCIATED PELVIC DISEASE

The frequency and character of the pelvic disorders in the histories of the present series of women are charted in table 17. Since uterine and ovarian disorders are of unequal significance, they have been separated. The occurrence of operations is also specifically noted since the previous existence of pelvic disease in these cases is particularly positive.

(*A*) *Uterine Disease.*—The uterine conditions are certainly less important than the ovarian, and yet certain points indicated by the tabulated statistics may have some bearing and must be stressed. 1. The series of conditions listed under uterine and labeled "others" include all cases of "inflammation of the womb" in which were probably a certain number of instances of salpingo-oophoritis. 2. A history of curettage for bleeding or sterility carries with it an implication of disturbed ovarian function. 3. The high incidence of fibroids is perhaps of considerable significance in linking tumors of the breast with the

TABLE 17.—*History of Gynecologic Disease*

	Premenopause											Menopause										Postmenopause										Total									
			Uterine					Ovarian					Uterine					Ovarian					Uterine					Ovarian					Uterine				Ovarian			
	Available Cases	Per Cent With Previous History of Gynecologic Disease	Total Uterine	Operations on Uterus	Fibroids	Displacements	Others	Total Ovarian	Operations on Ovary	Inflammations	Others	Available Cases	Per Cent With Previous History of Gynecologic Disease	Total Uterine	Operations on Uterus	Fibroids	Displacements	Others	Total Ovarian	Operations on Ovary	Inflammations	Others	Available Cases	Per Cent With Previous History of Gynecologic Disease	Total Uterine	Operations on Uterus	Fibroids	Displacements	Others	Total Ovarian	Operations on Ovary	Inflammations	Others	Available Cases	Per Cent With Previous History of Gynecologic Disease	Total Uterine	Operations on Uterus	Fibroids	Displacements	Others	Total Ovarian	Operations on Ovary	Inflammations	Others
Fibro-adenomas	19	26	3	2	1	1	1	3	2	3	0	3	(33)	1	0	0	0	1	0	0	0	0	0	.....	..	..	..	..	..	..	..	..	..	22	28	4	2	1	1	2	3	2	3	0
Painful nodules	19	47	5	0	0	1	4	4	3	4	0	1	(100)	0	0	0	0	0	1	0	0	1	0	.....	..	..	..	..	..	..	..	..	..	20	50	5	0	0	1	4	5	3	4	1
Chronic mastitis	28	43	8	3	1	3	4	5	2	4	1	22	36	6	5	3	1	2	3	2	2	1	2	(100)	1	1	0	0	1	1	1	0	1	52	42	15	9	4	4	7	9	5	6	3
Papillary tumors	4	75	3	3	1	1	1	1	0	0	1	4	(25)	0	0	0	0	0	1	1	0	1	1	(100)	1	0	0	0	1	0	0	0	0	9	55	4	3	1	1	2	2	1	0	2
Benign	70	37	19	8	3	6	10	13	7	11	2	30	37	7	5	3	1	3	5	3	2	3	3	(100)	2	1	0	0	2	1	1	0	1	103	42	28	14	6	7	15	19	9	13	6
Malignant	38	37	8	6	2	4	2	7	5	6	1	59	27	11	8	3	6	2	9	8	5	4	43	26	10	8	5	4	2	2	2	0	2	130	32	29	22	10	14	6	18	13	13	5

Note.—The column "others" includes: Benign: Uterine: "Inflammation of womb," "catarrh of the womb," 9 cases; curettage for sterility, 2 cases; curettage for metrorrhagia, 1 case; curettage for scanty menstruation, 1 case; dilatation of cervical stenosis, 1 case; curettage for discharge, 1 case. Ovarian: Oophorectomy, cause unknown, at 19 and 20, 2 cases; ectopic pregnancy, 2 cases; ovarian cyst, 1 case; "hemorrhage and ovary trouble," 1 case.

Malignant: Uterine: Adenocarcinoma of fundus, 3 cases; hysterectomy for "intestinal obstruction," 1 case; curettage for sterility, 1 case; curettage for scanty flow, 1 case. Ovarian: Ovarian cysts, 2 cases; oophorectomy for bleeding, 2 cases; ovary advised removed for pain, 1 case.

neoplasms of the other glandular organs connected with the sex function, for there is already a fairly well established association between uterine fibroids and tumors of the ovary, of the endometrium and of the thyroid.

As regards the endometrium, Kelly and Cullen found among a series of 1,400 myomas an associated carcinoma of the fundus in 1.7 per cent and an associated cervical in 1.3 per cent, and it must be remembered that were each association an accidental one the cervical carcinoma should have occurred from five to ten times as often. Winter, Hofmeier and several other writers have likewise drawn attention to this special association of myomas with endometrial cancer. Frankl alone denied this relationship, but the statistics on which his conclusions are based give a coincidence of myomas in cases of corpus carcinoma of only 9 per cent, a figure which appears to be surprisingly low. Mahle, for instance, reported a rate of association nearly four times as high.

The association of uterine myomas with papillary cystadenoma and cystadenocarcinoma of the ovary has been reported on by me.

Attention was drawn to the common coincidence of myomas and goiter as long ago as 1891 by H. W. Freund, and since then numerous other writers have made similar observations (Elsner, Ullmann, Aschner, Bauer, Pape). Estimates of the frequency of thyroid disease in association with myoma have varied from 28 to 100 per cent, depending apparently on the geographical location of the clinic.

The possibility exists, therefore, that the occurrence of a myoma is an indication of a special predisposition of those organs chiefly affected by the cycles of pregnancy and menstruation to form tumors, a predisposition that manifests itself most readily in the form of uterine muscular tumors, but also as new growths in various glandular organs and as an association of several tumors of different types more frequently than one would expect from a chance coincidence. The nature of such a possible relationship has been best illustrated by an article of Ballin and Moehlig in which they reported that among 100 patients consulting for goiter, 18 were found to have fibroid tumors and 4 tumors of the breast, while among 100 patients consulting for fibroid tumors 35 had also a goiter and 6 a tumor of the breast.

In the present series of mammary tumors, 16 of 233 patients who were questioned were aware of previous fibroid disease and of these all but 2 had had an operation for the condition. Examination in 66 cases added seven unsuspected myomas to the list so that the association with tumors of the breast of palpable fibroids or those requiring operation may be placed somewhere between 8 and 16 per cent. The incidence of myomas of appreciable size is therefore probably though not positively higher than for women in general.

Another observation of theoretically great significance is that cancer of the breast developed almost simultaneously with a carcinoma of the endometrium in three cases. The operations on the breast and uterus were performed at intervals of twenty-four, four and five months, respectively, the operation on the breast being performed first on the first two patients and that on the uterus in the last patient. The occurrence of these types of cancer in association in such frequency does not,

of course, represent the normal relationship, yet the fact of the similarity of the biology of these two forms makes one believe that their association is not entirely accidental. It is at least interesting to note that Smith and Bartlett and also Seliga and Esch have noted the occurrence of these two growths in association.

(*B*) *Ovarian Disease.*—As compared with the uterine conditions just discussed, the detection of some form of ovarian disease is much more direct evidence that the breast has been subjected to disturbing influences. The rôle of ovarian inflammation in the production of excessive premenstrual symptoms has been already discussed. The occurrence of ovarian tumors, on the other hand, may have the same significance as that of the myomas.

In the tabulated results of the study of previous ovarian disease, there appear marked differences in the type of pelvic disorder reported by the women of different ages. Now it has been stated that neoplastic changes in the breasts of young women should require the existence of a special congenital or acquired dysfunction while those of the older women might depend merely on the irregularities of function of the menopause or on the action of the changes of senility on the remnants of hyperplastic tissue. This point receives definite support from the fact that in both the benign and the malignant series about one fifth of the women of the young and middle age groups reported some form of antecedent ovarian disease and one tenth had actually been operated on for ovarian conditions, whereas among the older women this factor practically disappears from the histories.

As elsewhere in this paper, grounds for distinguishing between the specific etiology of malignancy and tumor growth in general are lacking, for there is no significant difference between the occurrence of pelvic disease in the history of the cancerous and noncancerous cases. Inflammatory disease of the ovary is a trifle more commonly associated with "painful lumps" than with any other form of new growth.

(*C*) *Results of Physical Examination of Pelvic Organs.*—Actual examination of the uterus and ovaries of about a quarter of all the patients revealed, as was to be expected, no constant gynecologic lesion. The observations noted in table 18 do illustrate, however, the universality of minor gynecologic lesions that are often symptomless. That this common pathologic process in the reproductive tract may affect the breast through the ovary is at least conceivable.

ASSOCIATED THYROID DISEASE

To see the significance of thyroid enlargement for the problem of hyperplasias and tumors of the breast, it is only necessary to recall that the physiologic conditions favoring thyroid enlargement are the same as those producing hypertrophy of the breast.

The incidence of thyroid enlargement in the various age and tumor groups is charted in table 19. Marked divergences between classes are very apparent. The younger women show this thyroid hypertrophy most frequently, and it is particularly in the type suffering from the so-called "painful nodule," the type with the marked menstrual irregularities, that a moderate increase in the size of the thyroid is of almost regular occurrence. The cases of carcinoma among the younger women also show a considerable though somewhat lower incidence of thyroid disease.

Some writers have contended that thyroid dysfunction is directly connected with the development of cancer. By comparing the average weights of the thyroid gland with the death rates for cancer in three different geographical regions, Bern, Munich and Kiel, Bayard was able

TABLE 18.—*Summary of Results of Gynecologic Examination*

Examined	Total	Group A	Group B	Group C
Benign	37	21	14	2
Malignant	29	5	21	3

Ovaries
Benign: Enlargement or inflammation, 8 [3 in confirmation of history]
Malignant: Enlargement or inflammation, 3 [1 in confirmation of history]

Fundus	Fibroids, Per Cent	Displaced, Per Cent	Enlarged, Per Cent	Atrophic or Hypoplastic, Per Cent	Normal, Per Cent
Benign	14	62	17	22	8
Malignant	22	35	8	22	14

Cervix	Laceration or Erosion, Per Cent	Enlarged, Per Cent	Atrophic or Hypoplastic, Per Cent	Normal, Per Cent
Benign	60	17	27	17
Malignant	41	10	31	26

to point out that in general the districts with the greater average thyroid weights were associated with a higher mortality from cancer. The difference in mortality rates for cancer between Italy and Switzerland illustrates the same point. Bayard attributed the higher rate for cancer to the general hypothyroidism.

Such an hypothesis as the one just noted is not offered in the present paper, but it is suggested that an endocrine or perhaps simply ovarian disorder is capable of producing a condition in the body similar to that physiologically present at puberty, and as a result growth processes of varying degrees take place simultaneously in breast and thyroid.

PHYSICAL EXAMINATION OF THE BREAST

The size, shape and consistence of the breasts and also the size and position of the tumors were carefully recorded descriptively and noted in the form of a diagrammatic sketch for each case. Such material lent

TABLE 19.—*The Association of Thyroid Disease with Tumors of the Breast*

	Premenopause							Menopause							Postmenopause							Totals						
				History Examination							History Examination							History Examination							History Examination			
	Available Cases	Total Thyroid Abnormality	Per Cent Thyroid Abnormality	Previously Noted Cases	Tumor Thyroid	Symmetrical Hypertrophy	Slight Fullness	Available Cases	Total Thyroid Abnormality	Per Cent Thyroid Abnormality	Previously Noted Cases	Tumor Thyroid	Symmetrical Hypertrophy	Slight Fullness	Available Cases	Total Thyroid Abnormality	Per Cent Thyroid Abnormality	Previously Noted Cases	Tumor Thyroid	Symmetrical Hypertrophy	Slight Fullness	Available Cases	Total Thyroid Abnormality	Per Cent Thyroid Abnormality	Previously Noted Cases	Tumor Thyroid	Symmetrical Hypertrophy	Slight Fullness
Fibro-adenomas	18	6	33	3	0	5	1	2	0	0	0	0	0	0	1	0	0	0	0	0	0	21	6	28	3	0	5	1
Painful nodules	18	15	83	7	0	12	2	1	1	(100)	0	0	0	1	0	0	.....	..	..	..	..	19	16	84	7	0	12	3
Chronic mastitis	26	9	35	1	0	3	6	18	3	17	2	2	0	1	3	0	0	0	0	0	0	47	12	25	3	2	3	7
Papillary tumors	4	3	75	1	0	0	2	2	1	(50)	1	1	0	0	1	1	(100)	1	1	0	0	7	5	71	3	2	0	2
Total benign	66	33	50	12	0	20	11	23	5	22	3	3	0	2	5	1	(20)	1	1	0	0	94	39	42	16	4	20	13
Malignant	33	9	27	4	2	5	2	55	8	15	4	2	3	3	42	2	5	0	1	0	1	130	19	15	8	5	8	6

TABLE 20.—*Size and Shape of Breast*

	Premenopause									Menopause									Postmenopause									Total								
		Size				Shape					Size				Shape					Size				Shape					Size				Shape			
	Available Cases	Large	Medium	Small	Per Cent Small	Pendulous	Medium	Erect	Per Cent Erect	Available Cases	Large	Medium	Small	Per Cent Small	Pendulous	Medium	Erect	Per Cent Erect	Available Cases	Large	Medium	Small	Per Cent Small	Pendulous	Medium	Erect	Per Cent Erect	Available Cases	Large	Medium	Small	Per Cent Small	Pendulous	Medium	Erect	Per Cent Erect
Fibro-adenomas	21	3	7	11	52	4	4	13	62	4	0	1	3	(75)	1	0	3	(75)	1	1	0	0	0	0	1	0	0	26	4	8	14	54	5	5	16	61
Painful nodules	21	4	11	6	29	6	2	13	62	1	0	0	1	(100)	0	0	1	(100)	0	..	..	..	.....	..	..	..	..	22	4	11	7	32	6	2	14	63
Chronic mastitis	29	8	12	9	31	15	10	4	13	24	10	13	1	4	17	5	2	8	3	1	2	0	0	2	1	0	0	56	19	27	10	18	34	16	6	11
Papillary tumors	6	0	3	3	50	1	1	4	67	4	2	1	1	(25)	2	1	1	(25)	1	0	0	1	(100)	1	0	0	0	11	2	4	5	45	4	2	5	45
Benign	77	15	33	29	38	26	17	34	44	33	12	15	6	18	20	6	7	21	5	2	2	1	20	3	2	0	0	115	29	50	36	31	49	25	41	36
Malignant	40	8	15	17	43	17	14	9	23	63	15	35	13	21	40	17	6	9	46	7	30	9	20	26	17	3	6	149	30	80	39	26	83	48	18	12

itself with difficulty to statistical tabulation, but led to a few definite impressions.

(*A*) *Size and Shape of Breast.*—In general, it may be said that the small, erect breast is found in childless and relatively underdeveloped women. Large and pendulous breasts occur in the opposite type, although excessive obesity and age may tend to produce the same effect without lactation. Table 20 is confirmatory of the charts on marriage and childbirth in that it shows the fibro-adenomas occurring chiefly in the small, erect breasts and chronic mastitis in the larger and pendulous ones. The cases of "painful lump" and those of early carcinoma appear less definitely related to breast form.

(*B*) *Type of Nipple and Areola.*—Although not charted, it may be said that the areola in the breast with fibro-adenoma is typically small and dark with a small well formed nipple. It is the virginal type approaching sometimes even the male form. In the cases of chronic mastitis the nipple is as a rule larger, the areola of much greater area, often light in color and less demarcated against the skin.

(*C*) *Consistence.*—The consistence of the unaffected breast is also of some interest, for one gains a decided impression that the structure of the tumor is related to the architecture of the breast tissue from which it is derived. In the great majority of the women with fibro-adenoma, the breast tissue was localized in the retro-areolar region and was frequently palpable as firm, lobulated masses of a consistence not unlike that of the fibro-adenoma itself. That such lobulated and slightly isolated tissue may often be removed under the impression that it is a true tumor has been convincingly demonstrated by McFarland. In the typical cases of chronic mastitis noted in this study, the breast tissue was neither concentrated nor lobulated but disposed diffusely or in the form of small nodules throughout most of the gross extent of both breasts. In practically all cases both breasts were involved, and from the sketches it appears that the points of chief localization of the process are usually strikingly symmetrical in the two breasts.

That the presence of carcinoma in one breast implies a special susceptibility to cancer formation in the other breast as well has been fairly well proved by Kilgore, who has computed statistics to show that any woman who has survived an operation for cancer of the breast for five years has from three to four times the chance of developing cancer in the remaining breast than would the average woman. These remote developments of cancer after operation are believed by Kilgore to be properly regarded as independent growths in the great majority of the cases, and it is likely that many of the more immediate involvements of the second breast should be similarly interpreted. The entire phenomenon of the bilateral development of cancer of the breast is slight additional evidence against an entirely local cause for mammary neoplasms.

(*D*) *Position of the Tumor.*—Particular attention in the examination of the patient was paid to the location of the tumor in the breast and especially to its relation to the nipple, since it was thought possible that different histologic forms might occur in different sections of the duct system and might even on that account have a different etiology. This attempt met with no success since it now appears probable that the actual distances from the nipple, as they were recorded, have a varying significance depending on the size and shape of the breast.

The occurrence of cancer with particular frequency in the upper outer quadrant has long evoked interest and has been explained on the supposition that drainage is most difficult and stasis most common in this region. Against this point of view may be mentioned two points. In the first place, it should be clear that in pendulous breasts the upper quadrant far surpasses all others in size and that with the nipple at the most dependent portion of the breast the lower quadrants practically disappear. But beyond this inequality of the size of the quadrants there is often clinical evidence that a greater concentration of glandular tissue exists in the tails of even normal breasts than elsewhere. Hence when cancer appears in the upper and outer quadrant, it is probable that it is merely developing in the region where the greatest number of cells are subject to the chance of malignant transformations.

NOTES ON GENERAL PHYSICAL CONSTITUTION

In the present study of tumors of the breast it had been hoped that anthropometric measurements could be employed such as those used so successfully by Draper, but the scope of this problem at once appeared beyond the efforts of a single worker. The records of weights and descriptive notes on certain points thought to have a special relationship to the reproductory system can therefore alone be offered.

(*A*) *General Body Form.*—It has frequently been suggested that certain types of persons have a special predisposition to develop tumors. Rokitansky drew attention to the antagonism between tuberculosis and cancer. Beneke, by actual measurements, concluded that cancer was a disease particularly of the broadly built, plethoric type of person. Beneke's work has been confirmed in recent years by the studies of P. Cohnheim on gastro-intestinal cancers and of Takata and Suzue on gynecologic carcinomas. Barker also has rather theoretically expressed the opinion that cancer was associated with good nutrition.

A more detailed consideration of the subject leads to certain possible reservations:

1. The constitutional type predisposed to neoplastic growth may be variable for different organs and for different forms of cancer. One would hardly expect cancer of the stomach developing on the basis of

gastric ulcer to be found chiefly in the broadly built and overnourished persons. On the other hand, there is some reported evidence that points to the association of overweight, particularly with certain of the forms of tumor that have been described, as allied to the neoplasms of the breast. Many writers, for example, have found that myomas occur especially in the well nourished (Hofmeier, Theilhaber, Pape, Beneke). Pinard noted the development of thyroid disease in association with weight increase, and Katz has made a similar observation on endometrial cancer.

2. The "cancer type" may be different for people of different ages, for Aschner wrote that cancer in the young is more apt to appear in the slender and undernourished type. Schmidt expressed the same opinion in special reference to gastro-intestinal cancer. A similar predisposition may exist for the benign growths, for Aschner likewise believes that myomas when they develop early favor slender types, with hypertrichosis and genital maldevelopment.

The few observations made on the physical constitution of the women in the present group are in general consistent with the views of the writers that have just been discussed.

(1) General Body Form: Table 21, in which is charted a summary of the examiner's impression of the general proportions of the patients, shows that the fibro-adenoma series in particular contains a very high percentage of undernourished women, while among the older patients with cancer there are an extraordinary number who were strikingly large and heavy.

(2) Average Weights: In table 22 are listed the average number of pounds which the patients reported as having been their weight when the tumor was first noted and before any loss from the effects of the disease itself had occurred. For comparison with this table there is appended a chart originally compiled by Weisse, showing the average weights of a very large number of women at different age levels. The women of this control were weighed in clothes and shoes corresponding in this respect to the state of dress under which the reported weights of the women with tumors were also obtained. For further accuracy, the mean age of the women of each pathologic and physiologic age group is given to aid in picking the proper weight for comparison from the chart of normal women.

A consideration of chart 21 shows that the young women with fibro-adenomas averaged 8 pounds (3.6 Kg.) less than the normal for their age. Those with malignant cases were from 4 to 6 pounds (1.8 to 2.7 Kg.) underweight. The women with chronic mastitis were at all ages a trifler overweight. Most striking of all, however, is the fact that among the older age groups with carcinoma, the average weights run

	Premenopause								Menopause								Postmenopause								Total							
	Available Cases	Immense	Heavily Built	Normal	Slender	Thin	Per Cent Above Normal	Per Cent Below Normal	Available Cases	Immense	Heavily Built	Normal	Slender	Thin	Per Cent Above Normal	Per Cent Below Normal	Available Cases	Immense	Heavily Built	Normal	Slender	Thin	Per Cent Above Normal	Per Cent Below Normal	Available Cases	Immense	Heavily Built	Normal	Slender	Thin	Per Cent Above Normal	Per Cent Below Normal
Fibro-adenomas	21	1	2	5	7	6	14	62	3	0	1	1	1	0	(33)	(33)	1	1	0	0	0	0	(100)	0	25	2	3	6	8	6	20	56
Painful nodules	19	0	3	6	5	5	16	53	1	0	1	0	0	0	(100)	0	0	..	..	..	..	..	.....	....	20	0	4	6	5	5	20	50
Chronic mastitis	28	3	8	7	7	3	39	35	24	5	10	5	2	2	62	17	3	1	0	1	1	0	(33)	(33)	55	9	18	13	10	5	49	27
Papillary tumors	6	0	2	2	1	1	33	33	3	0	2	0	1	0	(67)	(33)	1	0	0	1	0	0	0	0	10	0	4	3	2	1	40	30
Benign tumors	74	4	15	20	20	15	26	47	31	5	14	6	4	2	61	20	5	2	0	2	1	0	40	20	110	11	29	28	25	17	36	38
Malignant	38	4	10	13	7	4	37	29	62	10	30	11	10	1	64	18	40	12	19	12	6	0	63	12	149	26	59	36	23	5	57	19

TABLE 22.—*Average Weights at Time of Onset of Tumor*

	A_1, Puberty to 35			A_2, 35-40			B_1, 40-Onset of Menopause			B_2, Intra-menopause			B_3, 6 Mos.-5 Yrs. Postmenopause			C_1, 5-10 Years Postmenopause			C_2, Over 10 Years Postmenopause			Total		
	Available Cases	Average Age for Group	Average Weight for Group	Available Cases	Average Age for Group	Average Weight for Group	Available Cases	Average Age for Group	Average Weight for Group	Available Cases	Average Age for Group	Average Weight for Group	Available Cases	Average Age for Group	Average Weight for Group	Available Cases	Average Age for Group	Average Weight for Group	Available Cases	Average Age for Group	Average Weight for Group	Available Cases	Average Age for Group	Average Weight for Group
Fibro-adenomas	17	24.5	119	3	36.0	121	2	44.5	126.5	0	....	.....	1	43	152	0	....	.....	1	55	220	24	30.1	125.4
Painful nodules	18	26.8	125.8	0	....	.....	0	....	.....	1	50.0	145	0	....	.....	0	....	.....	0	....	.....	19	28.4	126.8
Chronic mastitis	20	29.0	135.3	7	37.5	131	2	40.0	139.0	15	45.4	147	3	46.7	168	2	53	156.5	1	81	112	50	37.0	140.8
Papillary tumors	0	....	.....	4	38.0	137	0	....	.....	3	43.7	147	0	....	.....	1	57	130.0	0	....	.....	8	40.5	140.0
Total benign	55	27.0	127.3	14	36.9	130.9	4	42.2	132.7	19	45.4	146.8	4	47.6	164.5	3	54.3	147.7	2	68	166	101	35.0	135.5
Malignant	16	29.8	125	19	36.8	144.8	16	43.0	159.5	19	45.4	147.4	20	50.5	152.9	21	55.1	153.5	22	60.4	159.9	133	46.7	151.8

Note.—The weights are those of the patients at the time of the tumor's onset as reported by the patient herself.

Table of Average Weights of Normal Women for Comparison

Age	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	All Ages
Weights	123	127	129	133	136	139	143	144	146	143	133

Note.—Life insurance statistics on 59,525 women weighed in clothes and shoes (Weisse).

from 2 to 20 pounds (0.9 to 9 Kg.) heavier than those of normal women at a corresponding age.

Were these observations corroborated, one must surely interpret them as indicating a predisposing effect of an abnormal (possible hyperthyroid) constitution in the young women with cancer of the breast and some special acquired glandular disposition in the older women that manifests itself as a tendency to excess deposit of fat. The statistics as given here are, of course, based on an exceedingly small number of cases, but some weight must be given them when it is remembered that they are in general confirmatory of previous studies on cancer in general and on uterine myoma, a tumor of the same body system as the breast.

(3) Changes in Weight: Table 23 has been prepared to show the history of weight variations during the ten years antedating the discovery of the tumor. It appears that of the women with carcinoma belonging to the early and middle age groups, over one-third had noted a gain of more than 10 pounds (4.5 Kg.), while the older women gave this history a trifle less frequently. These gains in weight are perhaps a little different from those occurring in the normal woman, but it is possibly significant that the increase is as frequently noted in the young woman as in those of the menopause age. An exception to the general rule of increasing weight is noted among the women with fibro-adenomas who in many cases reported losses in weight.

(*B*) *Race and Pigmentation.*—It has been asserted (Aschner) that cancer is peculiarly prevalent among dark haired and deeply pigmented persons, and furthermore, that various races have different degrees of susceptibility and immunity to certain types of tumor.

The results of observations on the color of the hair of the women in the present study (table 24) offer only one point worthy of note. The localized benign tumors show a special tendency to occur in the blonde and brown haired women and chronic mastitis and cancer in the black haired.

The racial distribution (table 25) undoubtedly accounts for this apparent tendency of persons with certain types of pigmentation to develop special forms of tumors, but whether this arrangement itself is indicative of actual racial predispositions or whether it is adventitious depending on an outside sorting of cases referred to the hospital is not clear. The peculiar predominance of Jewish women among the cases of chronic mastitis developing at the menopause and their almost complete absence from among the women with fibro-adenomas raises the question of whether functional difficulties at the climax may not be especially common in women of this race.

(*C*) *Hypertrichosis.*—The pattern of the facial and body hair is an accepted secondary sexual characteristic and should therefore be of con-

TABLE 23.—*Changes in Weight During Ten Years Preceding Onset of Tumors*

	Premenopause									Menopause									Postmenopause									Total								
		Gain				Loss					Gain				Loss					Gain				Loss					Gain				Loss			
	Available Cases	3-10 Lbs.	11-20 Lbs.	Over 20 Lbs.	Per Cent Over 10 Lbs. Gain	3-10 Lbs.	11-20 Lbs.	Over 20 Lbs.	Per Cent Over 10 Lbs. Loss	Available Cases	3-10 Lbs.	11-20 Lbs.	Over 20 Lbs.	Per Cent Over 10 Lbs. Gain	3-10 Lbs.	11-20 Lbs.	Over 20 Lbs.	Per Cent Over 10 Lbs. Loss	Available Cases	3-10 Lbs.	11-20 Lbs.	Over 20 Lbs.	Per Cent Over 10 Lbs. Gain	3-10 Lbs.	11-20 Lbs.	Over 20 Lbs.	Per Cent Over 10 Lbs. Loss	Available Cases	3-10 Lbs.	11-20 Lbs.	Over 20 Lbs.	Per Cent Over 10 Lbs. Gain	3-10 Lbs.	11-20 Lbs.	Over 20 Lbs.	Per Cent Over 10 Lbs. Loss
Fibro-adenomas	19	2	3	2	26	1	6	1	37	4	1	0	1	(25)	1	0	0	(0)	1	0	0	0	(0)	0	0	0	(0)	24	3	3	3	25	2	6	1	29
Painful nodules	18	1	4	4	44	5	1	0	6	1	0	0	0	(0)	1	0	0	....	0	..	..	..	....	..	..	..	....	19	1	4	4	42	6	1	0	5
Chronic mastitis	26	3	2	6	31	8	2	2	16	19	4	5	4	47	1	2	1	16	2	0	1	0	(50)	0	1	0	(50)	47	7	8	10	38	2	5	3	17
Papillary tumors	4	0	0	2	50	1	1	0	25	3	0	0	0	(0)	0	1	1	(33)	1	0	0	0	(0)	1	0	0	(0)	8	0	0	2	25	9	2	1	38
Total benign	67	6	9	14	34	15	10	3	19	27	5	5	5	37	3	3	2	18	4	0	1	0	(25)	1	1	0	(25)	98	11	15	19	35	2	14	5	19
Malignant	36	4	8	5	36	3	2	0	6	54	11	7	11	33	2	1	1	4	41	7	6	6	29	6	4	0	10	131	22	21	22	33	19	7	1	6

siderable importance in any attempt to correlate function of the sex gland with neoplasms of the reproductory system. Ovarian tumors have, for example, been frequently reported in association with a developing hypertrichosis (Halban), and the occurrence of myomas in young women with excessive hair has been mentioned (Aschner).

The existence of abnormal hair on various parts of the body is charted in table 26. It is probable that the presence of hair about the areola is a more important sign than hair on the face, for hair on the lip is a very common occurrence among the darker skinned people, and hair on lip and chin may be merely evidence of senescence.

The feature of possible importance in table 26 is the occurrence of a moderate amount of areolar hair in 28 and 50 per cent, respectively, of the women with fibro-adenomas and "painful nodules," and of marked breast or sternal hair in a smaller number. Such abnormalities

TABLE 24.—*Hair Color*

	Premenopause					Menopause					Postmenopause					Totals				
	Available Cases	Black	Brown	Blonde or Red	Gray or White	Available Cases	Black	Brown	Blonde or Red	Gray or White	Available Cases	Black	Brown	Blonde or Red	Gray or White	Available Cases	Black	Brown	Blonde or Red	Gray or White
Fibro-adenomas	17	6	6	4	1	1	0	1	0	0	1	0	0	0	1	19	6	7	4	2
Painful nodules	19	4	10	5	0	1	0	0	1	0	0	..	..	..	..	20	4	10	6	0
Chronic mastitis	25	17	3	4	1	17	8	1	2	6	2	1	0	0	1	44	26	4	6	8
Papillary tumors	3	1	2	0	0	3	2	0	0	1	1	0	0	0	1	7	3	2	0	2
Total benign	64	28	21	13	2	22	10	2	3	7	4	1	0	0	3	90	39	23	16	12
Malignant	31	17	8	5	1	51	22	5	6	18	40	8	0	0	32	122	47	13	11	51

were practically nonexistent among the older women with chronic mastitis or carcinoma and not at all frequent among even the younger patients with cancer.

HEREDITY

Estimates of the frequency of previous cancer in the family of women suffering from carcinoma of the breast have, according to Lane-Claypon, varied from 1.3 to 37 per cent. In her own most carefully checked series based on the cause of death of parents only, Lane-Claypon found the evidence for heredity rather slight, since the occurrence of cancer in one parent was 10.3 per cent for the cases of cancer and 8.1 per cent for the control women.

That such attempts to find evidence of a hereditary factor in cancer will always be unsuccessful seems highly probable, for there is practically no clinical evidence nor biologic reason for thinking that a

TABLE 25.—*Racial Distribution*

	Premenopause						Menopause						Postmenopause						Totals					
	Available Cases	North European	Jewish	Latin	Colored	Others	Available Cases	North European	Jewish	Latin	Colored	Others	Available Cases	North European	Jewish	Latin	Colored	Others	Available Cases	North European	Jewish	Latin	Colored	Others
Fibro-adenomas	18	12	1	3	1	1	3	1	1	0	0	1	1	1	0	0	0	0	22	14	2	3	1	2
Painful nodules	21	14	3	2	0	2	1	1	0	0	0	0	0	..	..	..	..	..	22	15	3	2	0	2
Chronic mastitis	28	12	10	3	2	1	23	5	15	0	1	2	3	1	2	0	0	0	54	18	27	3	3	3
Papillary tumors	6	4	2	0	0	0	4	1	3	0	0	0	1	1	0	0	0	0	11	6	5	0	0	0
Total benign	73	42	16	8	3	4	31	8	19	0	1	3	5	3	2	0	0	0	109	53	37	8	4	7
Malignant	41	18	12	7	1	3	62	32	17	3	2	7	49	27	11	3	5	3	152	78	40	13	8	13

TABLE 26.—*Hypertrichosis*

	Premenopause								Menopause								Postmenopause								Totals							
		Face				Breast				Face				Breast				Face				Breast				Face				Breast			
	Available Cases	Slight	Moderate	Marked	Per Cent Moderate Marked	Slight	Moderate	Marked	Per Cent Moderate Marked	Available Cases	Slight	Moderate	Marked	Per Cent Moderate Marked	Slight	Moderate	Marked	Per Cent Moderate Marked	Available Cases	Slight	Moderate	Marked	Per Cent Moderate Marked	Slight	Moderate	Marked	Per Cent Moderate Marked	Available Cases	Slight	Moderate	Marked	Per Cent Moderate Marked	Slight	Moderate	Marked	Per Cent Moderate Marked
Fibro-adenomas	18	1	5	3	44	1	3	2	28	2	0	0	1	(50)	0	1	1	(100)	1	0	1	0	(100)	0	0	0	0	21	1	6	4	47	1	4	3	33
Painful nodules	18	1	7	0	39	3	6	3	50	1	0	1	0	(100)	0	0	0	(0)	0	..	..	..	.....	..	..	..	..	19	1	8	0	42	3	6	3	47
Chronic mastitis	25	0	12	1	52	3	4	1	20	18	1	7	2	50	1	1	0	5	3	1	1	0	(33)	0	0	0	0	46	2	20	3	50	4	5	1	13
Papillary tumors	3	2	0	0	0	0	0	0	0	3	0	2	0	(67)	0	0	1	(33)	1	0	0	0	0	0	0	0	0	7	2	2	0	29	0	0	1	14
Total benign	64	4	24	4	44	7	13	6	30	24	1	10	3	53	1	2	2	16	5	1	2	0	(40)	0	0	0	0	93	6	36	7	46	8	15	8	24
Malignant	31	7	3	6	29	2	3	1	13	52	10	7	4	21	1	0	1	2	39	19	6	2	21	0	0	0	0	122	36	16	12	23	3	3	2	4

tendency to the inheritance of cancer in general exists. It is, for example, impossible to believe that a history of squamous carcinoma of the tongue in the grandfather of a woman with cancer of the breast is of any importance. A history of carcinoma of the endometrium, of a fibro-adenoma of the breast or even of a myoma of the uterus is possibly of significance, while a previous case of cancer of the breast in the family is probably worthy of serious consideration.

Certain single striking instances of the multiple occurrence of specific forms of cancer in a family have from time to time been published, and among these, instances of the inheritance of breast cancer are frequent. There is, for example, the family tree published by Broca in which sixteen cases of cancer occurred in four generations among thirty-three persons and of these sixteen, eleven were localized in the breast, three in the liver (metastatic?), one in the uterus and one in the stomach. The case of gastric cancer was the only one of the group to occur in a male.

A still more extraordinary instance of apparent heredity is that reported by Leschcziner of a mother and three daughters who each developed breast lumps early in life at the respective ages of 21, 14, 24 and 19. Three eventually died and the fourth had recently been operated on at the time of the report. In each the diagnosis was carcinoma and in the three in which the sections could be studied the tissue showed adenocarcinoma with some colloid degeneration.

In a study of the family histories of the present group (table 27) it was found that 6 per cent of the women of the entire series (271 cases) knew of a previous case of cancer of the breast in their family. It is also to be noted that five of the patients reported two cases of previous mammary neoplasm in their family (table 27).

It was thought that perhaps next to actual cancer of the breast some significance might be attached to the previous occurrence of other forms of genital tumors, but the table fails to give evidence of this. The question of fibroid tumors and goiters in the family was not, however, carefully gone into with each patient.

One rather striking fact is that the family history of cancer is rather higher in percentage among the women with benign tumors of the breast than those with malignant. This relationship is further support of the contention that if a hereditary factor exists, it is in the nature of a predisposition to irregular proliferative processes in general and not to malignancy in particular.

An attempt to correlate the physiologic era of development of cancer in the patient with that in which the relative developed her tumor failed to lead to any results. The family of Leschcziner showed apparently an inheritance specifically dependent on certain constitutional

TABLE 27.—*Occurrence of Neoplasms in Families of Patients*

	Premenopause								Menopause								Postmenopause								Totals							
		Breast		Pelvis		Others				Breast		Pelvis		Others				Breast		Pelvis		Others				Breast		Pelvis		Others		
	Available Cases	Malignant	Benign	Malignant	Benign	Malignant	Total Cases With Cancer in Family	Per Cent With Cancer in Family	Available Cases	Malignant	Benign	Malignant	Benign	Malignant	Total Cases With Cancer in Family	Per Cent With Cancer in Family	Available Cases	Malignant	Benign	Malignant	Benign	Malignant	Total Cases With Cancer in Family	Per Cent With Cancer in Family	Available Cases	Malignant	Benign	Malignant	Benign	Malignant	Total Cases With Cancer in Family	Per Cent With Cancer in Family
Fibro-adenomas	17	2	1	1	1	3	6	35	1	0	0	0	0	0	0	(0)	1	0	0	0	0	0	0	(0)	18	2	1	1	1	3	6	33
Painful nodules	16	2	1	1	1	0	3	19	1	0	0	0	0	1	1	(100)	0	..	..	..	..	..	..	....	17	2	1	1	1	1	4	23
Chronic mastitis	27	1	1	1	2	3	5	18	15	2	1	1	1	5	8	53	3	0	0	0	0	2	2	(67)	45	3	2	2	3	10	15	33
Papillary tumors	2	0	0	0	0	1	1	50	3	0	0	0	0	0	0	0	1	0	1	0	0	0	0	(0)	6	0	1	0	0	1	1	16
Total benign	62	5	3	3	4	7	15	28	19	2	1	1	1	6	9	47	5	0	1	0	0	2	2	(40)	86	7	5*	4	5	15	26	30
Malignant	44	1	2	1	0	1	3	7	33	4	0	2	2	9	15	45	41	5	0	0	0	3	8	20	118	10	2	2	2	8	20	18

* Three of the cases listed as benign were probably cancer.

Note.—Of all the patients with previous cancer of the breast in their family, 4 (2 in benign and 2 in malignant series) had had two previous cases of cancer of the breast in their families and a fifth gave a family history of one previous case and one benign new growth.

peculiarities of puberty. A similar relationship might conceivably exist between cancer and certain hereditary peculiarities of response to the menopause.

The hereditary factor in mammary tumors appears undoubtedly to be a predisposition only, suppressed or brought to the surface by the character of the physiologic processes that the patient's life has accidentally brought to her breast. It is difficult to imagine on what other basis such a predisposition can rest than on an hereditary anomaly of the constitution of the reproductory system.

THE HISTOLOGIC FORM OF CANCER OF THE BREAST IN RELATION TO ETIOLOGY

A part of the original plan of this study had been to separate the different microscopic forms of cancer of the breast from each other and to examine individually the etiology of various types. Unfortunately, it was found that in only a small proportion of the cases was there available pathologic material suitable for making the finer diagnosis of special types of cancer.

That such a study might shed a light on the cause of cancer of the breast is clear from the following considerations:

(*A*) *Form and Location.*—The various sections of the breast, large ducts, small ducts and acini, are physiologically different in their reactions, variably responsive to endocrine stimulation and diversely subject to chances of inflammation. The striking contrast afforded in the uterus by the biology of cervical and fundal cancers is illustrative of the diversities that may exist between the strictly parenchymatous and the ductal portions of an organ. That Paget's disease of the nipple is an essentially different type of lesion from the adenocarcinoma of the finer ducts and acini is probable. Differences dependent on their points of origin may also exist between the etiology of many special forms. It is for these reasons that, although endocrine influences appear to be important factors in initiating atypical cell proliferation in the breast, the idea of other agencies being sometimes effective cannot be discarded.

(*B*) *Form and Physiologic Phase.*—Beside the question of whether histologic form is related to the site of origin of the tumor, there is the problem of whether tumor architecture is connected with the physiologic phase in which the breast happens to exist at the time of the genesis of the new growth.

The few cases that could be assembled for this study afford a little evidence to show that certain tendencies do exist for different forms of cancer to develop under special circumstances (table 28).

(1) Age: Adenocarcinoma is the predominant tumor of early life but also occurs in the aged. Other forms are scattered, but, in general,

the less differentiated types appear later in life. It is disappointing, however, to find that there is no sharply defined type of distribution, since examples of any variety may be found at any age.

(2) Development: The adenocarcinoma group shows the highest percentage of single and sterile women and the greatest frequency of nursing failures. On the other hand, it is apparently the women whose breasts have had at one time the fullest functional development that produce tumors with the least differentiation.

(3) Position of the Tumor: Attempts to relate histology with the position of the tumor in the breast met with no success. The study of

TABLE 28.—*Histologic Type of Cancer of the Breast in Relation to Etiology*

	Total	Age			Breast Development					Size of Breast			Shape of Breast			Location of Tumor			
	Total	Premenopause	Menopause	Postmenopause	Single Women	Sterile Women	Children, No Lactation	Children, Poor Lactation	At Least One Normal Lactation	Large	Medium	Small	Pendulous	Medium	Erect	Peripheral	Intermediate	Central	Undeterminable
Adeno-carcinoma	20	9	5	6	3	3	2	4	8	2	10	6	9	8	1	2	5	2	11
Sweat gland carcinoma	5	0	3	2	1	0	0	2	2	1	3	1	3	2	0	1	0	0	4
Alveolar carcinoma	11	3	6	2	1	1	0	2	7	3	6	2	6	4	1	5	1	1	4
Duct carcinoma	6	2	2	2	1	1	0	0	4	3	1	2	3	2	1	0	1	1	4
Simplex carcinoma	9	1	5	3	0	0	1	1	7	2	6	1	7	2	0	1	1	0	7
Medullary carcinoma	5	3	1	1	2	0	0	0	3	0	2	3	3	0	2	0	1	0	4
Infiltrating carcinoma	4	2	1	1	0	0	1	1	2	1	1	2	2	2	0	1	1	0	2
Fibrocarcinoma	4	1	1	2	0	0	0	1	3	2	1	1	2	1	1	2	1	0	1
Scirrhus carcinoma	3	0	1	2	0	1	0	0	2	1	2	0	3	0	0	1	0	1	1
Total	67	21	25	21	8	6	4	11	38	15	32	18	38	21	6	13	11	5	38

this aspect of the problem must apparently be accomplished in the laboratory for the clinically determined location gives no indication of the point of origin of the tumor relative to the duct system.

From this brief survey it appears that adenocarcinoma tends to occur in the younger women, and like the fibro-adenomas, in women with less well developed breasts. According to Ewing, most adenocarcinomas arise from areas of chronic mastitis, cystadenoma or papillary adenoma, which perhaps explains the early incidence of this type at the time when benign forms are actively growing. The response of certain of the less malignant (more differentiated?) forms of inoperable cancer to oophorectomy as reported by Beatson and his followers suggests further that this type is closely related to the benign tumors in a physiologic as well as a structural sense.

That the opposite of this theory may also be true, namely, that the less differentiated forms of cancer of the breast are less related to the benign lesions and hence perhaps governed by different etiologic factors such as senile involution, trauma and infection, remains a possibility.

RÉSUMÉ

That the breast epithelium is normally responsive throughout life to stimulation by the internal secretion of the ovary has been shown at considerable length in the first sections of this paper. At the same time it must be clear that when the ovarian activity manifests itself in a regularly recurring cycle proliferative and regressive processes in the genital organs balance each other so nicely that during normal adult life no actual growth takes place.

From the point of view of clinical observation, the condition necessary for breast growth is the presence of a partially active ovary which is not producing a menstrual cycle. Such is the normal state before puberty and during pregnancy. A similar intermediary stage of ovarian activity must exist for a longer or shorter time at the menopause as the sex glands pass from the state of full activity to complete extinction.

Beside these relatively normal occasions in which breast proliferation may occur, there are certain abnormal endocrine states in younger women which may closely simulate one of those just noted and in which conditions also appear to be correct for breast growth. The first of these is seen in women whose reproductory system never completely developed and whose organs and body form resemble those of a girl at puberty. The second is that of acquired hypofunction of the ovary, manifesting itself in increase of weight, menstrual disorders and other symptoms usually associated with the menopause.

It has been my purpose in this paper to assemble the evidence in favor of the theory that tumors of the breast of practically all varieties are not only logically but also actually dependent on abnormal variants of the physiologic endocrine states that normally produce breast growth.

Clinical observations indicate that special forms of tumor of the breast tend to be associated with particular types of the disorders that have been described.

A. The fibro-adenoma occurs typically in breasts that are a part of a generally underdeveloped reproductory system and under conditions in the body somewhat similar to those existent at the time of the development of the breast at puberty. This view is consistent with the highly organic character of the histology of this tumor and the fact that it is frequently a rather faithful reproduction of the normal gland. It is also not incompatible with the theoretical view that the fibro-adenomas are derived from previously undeveloped "fetal" rests.

The reasons for believing that the women of the fibro-adenoma group are backward in development and are suffering from a special form of glandular derangement are the following:

1. The great majority are unmarried.

2. Few have had children.

3. Among those who have borne children, few have nursed them successfully.

4. There is a high incidence of irregular menses, especially of the shortened interval type, and the duration of the periods tends to be long. These irregularities date from puberty and are not acquired.

5. Dysmenorrhea is common, and being present is indicative of hypoplasia uteri.

6. Premenstrual breast pain is marked and, as a rule, has been present since puberty.

7. The incidence of acquired pelvic disease is low.

8. The thyroid is often slightly enlarged, a condition frequently met with in adolescence. The conception of Biedl that there is thyroid dominance during childhood until its activity is suppressed by the maturing sex glands may be cited to indicate further that the women of this fibro-adenoma group are still for all practical purposes in an adolescent stage.

9. The breasts are small and erect with small nipples and areolae and often with a little excessive hair.

10. The patients themselves tend to be slender and a little underweight, possibly further proof of their "adolescent" state.

B. Chronic mastitis occurs as a secondary proliferative process in breasts that have at one time attained a considerable degree of development but which have passed through an involutional period. It arises under conditions of irregular, but apparently, as a rule, declining ovarian activity. Such conditions exist typically during the years preceding the cessation of menstruation at the climax but also in younger women with a disturbance of the ovarian function. These views are consistent with McFarland's theory that the cysts are evidence of an incomplete involution after a lactation hypertrophy and with Cheatle's teaching that the essential feature of the disease is a hyperplasia. It is, of course, clear that "chronic mastitis" is a misnomer, some such term as "fibro-adenosis" being preferable in my opinion. (Note Semb's use of word "fibro-adenomatosis.")

The reasons for believing that chronic mastitis is a secondary proliferative process occurring in involuting breasts under the influence of irregular ovarian function are the following:

1. The greater number of the women with this disease are married.

2. The majority have had children.

3. The fact that the percentage of nursing failures was relatively low indicates that the breasts were once normal.

4. A considerable number of cases occur just before the menopause or in actual association with the menstrual irregularities preceding cessation. The frequency of menstrual abnormalities in the younger women indicates that a subnormal ovarian function exists in these cases which is potentially similar to that of the menopause.

5. Dysmenorrhea is rare.

6. Premenstrual breast pain is unusual in the older women with chronic mastitis, but is fairly frequent in the younger women.

7. The incidence of acquired pelvic disease is fairly high.

8. Thyroid hypertrophy is unusual.

9. The breasts are as a rule pendulous with large nipples and wide but often colorless areolae.

10. The body weight tends to run a little above the normal for the age, and recent increases in weight are common.

C. The "painful nodules" are at best an ill defined and somewhat arbitrarily collected group. The more localized examples are difficult to separate from the fibro-adenomas, and the more diffuse from the cases of chronic mastitis. It should be noted in particular that in the early age group many of the cases of chronic mastitis, so classified on account of the palpably diffuse nature of the process, should perhaps etiologically have been placed with the cases of painful lump.

In general, it may be said that the examples of this entity often give the impression of being partly dependent on a slight developmental deviation from the normal, but the essential feature is the presence of a new proliferative stimulus being applied to a breast which is still in the period of full maturity and in which involutional changes are decidedly not prominent.

The reasons for taking this point of view are the following:

1. The majority of the women are young.

2. Only about half of the women have had children.

3. Success in nursing has not been as universal as in the cases of the women with chronic mastitis.

4. Abnormal menstruation, often of an acquired type, is more common than with any other form of breast neoplasm in young women.

5. Dysmenorrhea is fairly frequent but not so prominent as in the case of the patients with fibro-adenoma.

6. The premenstrual breast signs are extremely marked, a fact indicative of excessive corpus luteum stimulation.

7. The incidence of acquired pelvic disease, especially of an inflammatory character, is high.

8. The thyroid is almost constantly slightly full.

9. The form of the breast offers nothing characteristic.

10. The general body form and weight tend toward slenderness.

The conditions favorable to the formation of these growths have been discussed as if only three distinct types existed. Such is obviously not the case, for it has already been pointed out that morphologic varieties of tumor tend to be connected by transitional forms and the much less tangible conditions of etiology are, as might have been expected, still less sharply defined. Furthermore, since the characteristics of etiology of tumor forms as outlined are based entirely on percentages which never approach the hundred mark, it must be evident that they are representative of tendencies only.

D. The relation of the ovarian function to the formation of malignant tumors of the breast is much less clear than it is for the benign forms, yet two facts derived from the histologic studies of the pathology of the breast indicate that for some cancers at least all that has been said about the benign tumors may be said about the malignant tumors also. The first of these points is the debated theory of the origin of malignant tumors from the benign ones, and the second is the absence of any sharp histologic line between differentiated adenocarcinomas and relatively actively growing benign tumors.

In order to relate the development of cancer to abnormalities of the ovary, certain suppositions are necessary.

1. In women in whom malignant growths develop before the menopause, cancer may arise under various conditions of abnormal ovarian activity. A single type of abnormality will not explain it. Thus it must be assumed that in different women cancer may appear under the conditions noted for the fibro-adenomas, for the "painful nodules" or for chronic mastitis. In other words, it may be related to the disturbances ot ovarian activity incidental to puberty or to an ovarian anomaly describable as a delayed puberty, to an unknown disturbance during pregnancy, to the irregularities of the menopause or to a hypo-ovarianism in younger women that simulates the menopause state. Granted this supposition that cancer may be related to any of these phases of disturbed ovarian activity, practically every case among the younger women in the present group could be explained.

2. The late carcinomas of the breast can be related only to the ovarian function by assuming that they are derived from benign or malignant cell rests quiescent since the time preceding the extinction of the ovarian influence. Such a theory is not to be lightly rejected since if carcinoma is derived from benign hyperplastic epithelial tissue, its ultimate origin must date back to the menopause, for it appears that benign processes rarely, if ever, have their inception after the ovary has completely ceased to be active.

Another reservation is also to be made, for it must be clear that the indicated conclusions of the present study pertain only to the origin of tumors in general and not at all to the cause of malignancy in particular, since practically all the anomalies of the sexual function that were noted were found equally frequently in the benign and malignant series. The point reached, therefore, is that at which most clinical studies on the genesis of cancer, actually though not always admittedly,

terminate. It is the point where one must somewhat lamely postulate that the cause of cancer is the same as that of the precancerous lesion with the possible addition of the accumulative effects from a longer or stronger stimulation by the original agent or the hypothetic coopertion of an individual or age predisposition of the tissues.

In spite of many reservations there is considerable evidence that ovarian dysfunctions are concerned in the production of cancers of the breast.

1. The fact that most reports indicate a greater predisposition among unmarried women indicates that the cases, if any, due to inflammatory conditions of the puerperium are rare since they must weigh so little in the gross statistics.

2. The lower fertility among women with cancer, as reported by several writers, is suggestive of relatively frequent pelvic disease.

3. Failure to nurse in a normal manner, a factor often stressed by students of the etiology of cancer of the breast, appears from an investigation of the causes of these failures to be due almost entirely to insufficient secretion, an internal factor connected with the constitution of the reproductory system.

4. A large percentage of the cases of cancer of the breast occur just before, during or immediately after the menopause when abnormal stimulation of the breast by the ovary may be assumed. Among the younger women with cancer of the breast many have suffered from a recent change in the type of their menstrual periods, an indication of changing conditions in the ovary. Among the older women, the growths may represent the gradual malignant transformation of abnormal epithelial tissues that took origin at the time of the menopause.

5. Dysmenorrhea is of moderate frequency among the younger women with cancer of the breast, indicating that certain of these early cases may have been produced under conditions similar to those under which fibro-adenomas arise.

6. Premenstrual breast pain is frequently a symptom noted as having appeared for the first time shortly before the discovery of the tumor and is evidence of a recently acquired, excessive corpus luteum effect on the breast.

7. The history of an acquired pelvic disease or of a major gynecologic operation is met with extraordinarily often in the study of patients with breast cancer and suggests the possibility that abnormal proliferation in the breast may at times depend on an ovarian function disturbed by the results of pelvic inflammations or congestions.

8. The thyroid often shows some abnormality, such as diffuse enlargement in the younger or nodular goiter in the older patients. The significance of this change rests on the probable existence of a common stimulus producing the two tumor forms, since under physiologic conditions both organs usually hypertrophy simultaneously.

9. Cancer occurs in all types of breasts, but in the younger women it is more common in the small erect breast, similar to that which appears to be especially susceptible to the fibro-adenoma, while in the older women it occurs chiefly in breasts which are also the seat of chronic mastitis.

10. The body weight in cases of breast cancer was below the average for normal women in the early age groups and above the average in the later period. In this respect the women with cancer followed the tendency noted on the one hand for the fibro-adenomas, and on the other for the cases of chronic mastitis.

To be in harmony with the theory that an internal, endocrine disturbance is the cause of tumors of the breast, the factor of heredity must be effective through the medium of a special type of inherited genital constitution which is so predisposed as to produce atypical breast proliferation in certain of the physiologic eras of life. If such is the case, no tumors are significant in the family history except those of the breast and perhaps of the other organs connected with reproduction. On the other hand, it appears that the hereditary factor is not always specific as to the exact form which the tumor of the breast may assume, but manifests itself as carcinoma in one generation and as a benign tumor in another.

CONCLUSION

The parenchyma of the breast has been shown to depend on the sexual cycle for all its normal variations of structure and to be capable of rapid growth and transformations under certain physiologic conditions of ovarian activity. In this respect the breast is similar to the endometrium, the thyroid and certain ovarian structures. Pathologically, the various forms of tumor of the breast have their counterparts in the tumors of the three organs mentioned and of the prostate. What clinical observations can be collected from the literature and from this study of 271 cases indicate that etiologically the tumors of the breast, including carcinoma, are closely related to those of the endometrium, thyroid and ovary, are somewhat allied to myomas of the uterus and are in a way equivalent to tumors of the prostate. The tumors of these five organs, therefore, form a group, the etiology of whose members shows many points of mutual resemblance. To attempt to relate inflammatory accidents of lactation to cancer of the breast is to classify it etiologically with cancer of the cervix, which on both inductive and deductive grounds appears unjustifiable.

It is possible that the contrast afforded by the causes of origin of these two common types of new growth may lead to the formulation of a general principle. Such a principle would amend the teaching that cancer results from chronic irritation by adding that the stimulus must as a rule be of the same type as that to which the particular tissue is biologically best adapted to respond with proliferation. Such a conception would appear, superficially at least, to reconcile the conflicting theories of numerous authors, who have formed their opinions of the causes of cancer from the study of the new growths of entirely different tissues. With this view it would be entirely consistent for mechanical or chemical irritants to produce cancerous changes in the protective epithelial cells covering the surface of the body and lining the walls of the intestinal tract, for an infectious agent to induce new growth in lymphoid, myeloid or granulomatous tissue. for trauma to produce tumors by evoking the reparative function of fascial and osteogenic cells

and finally for hormonal influences to be effective in producing hypertrophy, hyperplasia and neoplasms in the breast and other organs whose normal growth processes are under endocrine control.

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INDUCED PARALYSIS OF THE DIAPHRAGM*

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Induced paralysis of the diaphragm imitates spontaneous paralysis, which is a natural protective reaction to divers pleuropulmonary irritations. The capacity of the thoracic cavity of the side affected, or of both sides if the paralysis is bilateral, is reduced by the upward displacement of the diaphragm.

A further reduction frequently results from a correlated increased declivity of the ribs and narrowed intercostal spaces (figs. 1 and 2). Moreover, the excursions of the ribs are restricted. Induced and spontaneous paralysis may be incomplete or complete, unilateral or bilateral, transient, temporary or permanent.[1]

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* The experimental observations on which the clinical work was based were conducted in the Ambulance de L'Ocean at LaPanne (1917), the Central Laboratories of the A. E. F. (1918), and at Columbia Hospital (1919-1920) under grants from the American Red Cross. The clinical work was done in various hospitals for nontransportable wounded of the First Army, A. E. F., in the Muirdale Sanitarium for Tuberculosis of Milwaukee County, in Mount Sinai and Columbia Hospitals, Milwaukee.

Evidence for statements made in this communication can be found in the following: Yates: Wounds of the Thorax, in Oxford Surgery, London, Oxford University Press; Wounds of the Chest, in the Medical Department of the U. S. Army in the World War, 1927, vol. 11, pt. 1, pp. 343-442; Effects of Acute and Chronic Pneumothorax, Am. J. M. Sc. **165**:1, 1923; The Significance of Vital Capacity in Intrathoracic Therapy, Arch. Surg. **10**:477 (Jan.) 1925; The Significance of Vital Capacity in Intrathoracic Therapy, ibid. **12**:257 (Jan.) 1926; Rationale of Operations Helpful in Promoting Recoveries from Pulmonary Tuberculosis, ibid. **14**:369 (Jan.) 1927; Pulmonary Tuberculosis, ibid **19**:1122 (Jan.) 1929. Yates and Raine: Diseases of the Lymphatics, in Practice of Surgery, Hagerstown, Md., W. F. Prior Company, 1929, vol. 3, chapter 9.

1. Upward displacement is caused by the action of negative intrapleural pressures and positive intra-abdominal pressures on a more or less inert diaphragm, unless pleuritic adhesions at the base are strong enough to prevent it. Increased declivity of the ribs and narrowing of the intercostal spaces is more constant and greater if the muscle is atonic as well as paralyzed. This effect on the levator-costal and intercostal muscles is apparently produced by some reflex inhibition, probably through the sympathetic nerves. Paralysis and consequent elevation of the diaphragm affect animals with thin pleurae and those with thick pleurae dissimilarly. Human beings have thick pleurae. The mediastina of animals with thin pleurae are neither air-tight nor water-tight. The mediastina of those with

Occasionally a transient bilateral paralysis is induced to arrest singultus, or a transient unilateral paralysis is used to facilitate transabdominal repair of diaphragmatic hernia. Commonly, temporary and permanent paralysis and atonicity are induced for purposes to be discussed later because of the following responses:

Reduction in the capacity of the thoracic cavity imposes a corresponding diminution in the volume of the lung. Restricted movements of the parietes limit the excursions of the lung to those slightly above and below the level of mean inflation.

Reduction of the volume of the lung approaches but does not reach the position of collapse (which occurs if negative pressures are abolished) when complete paralysis and atonicity are induced and the ascent of the diaphragm is not impeded by adhesions. Under these conditions the lungs and visceral pleura of human beings and animals with thick pleurae receive the largest unit volumes of blood through the bronchial vessels, and the lungs receive the largest volumes of blood through the pulmonary vessels.[2] Both blood volumes are delivered with less than usual cardiac labor because peripheral intravascular resistance is so nearly minimal. Material restriction of pulmonary excursions curtails the dissemination of noxious substances from pleuropulmonary lesions and does not interfere with healing, which can be almost scarless.

Thus induced paralysis, which, be it reemphasized, is an imitation or rather a reproduction of natural protective reaction to some pleuropulmonary irritations, accomplishes two extremely beneficent results. It shields the subjects from intolerably rapid dissemination of toxic products, bacteria and tumor cells from inflammatory and neoplastic lesions. The maximum units of blood delivered assure that the lungs and visceral pleura will realize the utmost of their power of resistance, defense and repair.[3]

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thick pleurae are both air-tight and water-tight. Elevation of one side of the diaphragm in the former reduces intrapleural negative pressures equally in both sides of the thorax; in the latter, only in the side affected. Moreover, the compensatory emphysema which occurs automatically with unilateral diaphragmatic paralysis in the contralateral lung prevents displacement of the mediastinum toward the unaffected side if the circulatory apparatus is competent; it may even cause displacement toward the affected side.

2. Andrus and Wilson (Arch. Surg. **19**:1205 [Jan.] 1929) showed that this effect is produced in both lungs of animals with thin pleurae (dogs) if one side of the diaphragm is paralyzed.

3. Resistance, defense and repair are produced by the activities of tissue cells, supported, stimulated and supplemented by the cellular and noncellular constituents of the blood delivered to them. If they are adequate, they confer insusceptibility. If slightly less adequate, disease is inaugurated but recovery occurs. If they are more inadequate, death is inevitable. Therapy is successful as it increases the quantity of blood delivered to lesions and improves the quality of blood in circulation, and, when necessary, restores its volume.

These benefits are purchased at a price. Paralysis of one side of the diaphragm reduces vital capacity upward of 10 per cent even when the lungs are little affected and the myocardium is competent. Vital capacity measures the efficacy of external respiration which determines the capacity of a person to work and to survive. Paralysis of both sides of the diaphragm more than doubles the handicaps of unilateral paralysis.

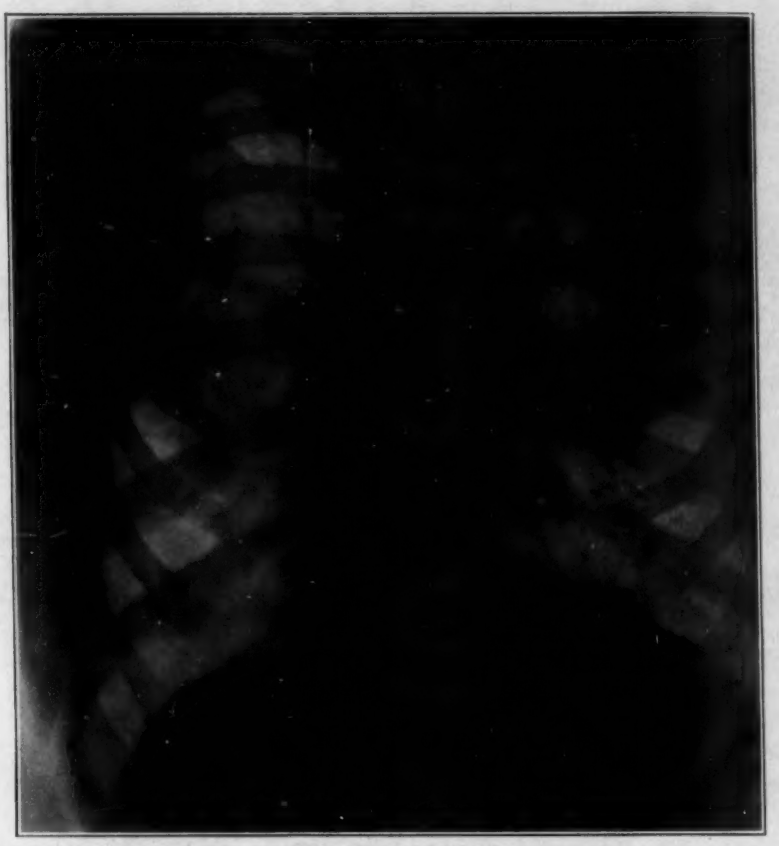

Fig. 1.—J. W., Muirdale Sanitarium, March 25, 1924, aged 28. Roentgenogram taken at the end of inspiration. There is limited spontaneous paresis of the right side of the diaphragm, and coincidental narrowing of the intercostal spaces on the right side. Phrenemphraxis performed on April 8, 1926, induced complete paralysis but not atonicity. Severe crushing was employed to protract effect.

The technical problems involved in the induction of paralysis are now obvious, namely: how to induce complete paralysis and atonicity simply and dependably and how to induce transient, temporary and permanent paralysis so that the handicaps imposed need not exceed benefits conferred.

Motor impulses are transmitted to the diaphragm in human beings with rare, if any, exceptions, through the phrenic nerves and their aberrant or accessory branches. Some of the impulses that maintain the tonicity of the diaphragmatic muscles are transmitted through fibers in the sympathetic nerves. Numerous anatomic studies have revealed that aberrant and accessory branches arise from phrenic nerves and from

Fig. 2.—J. W., Muirdale Sanitarium, Dec. 20, 1929, aged 34. Roentgenogram taken at the end of inspiration. There is incomplete recovery of motion of the right side of the diaphragm. Increased declivity of the ribs and narrowing of the intercostal spaces (right) has reduced capacity of the right side of the chest materially and has induced obvious compensatory emphysema in the left lung. The mediastinum was thereby displaced slightly to the right.

their constituent third, fourth and fifth cervical roots in more than one half of all people, and that these branches may take divers pathways to reach the diaphragm. Some run independently and are aberrant; others

fuse with the nerve to the subclavius muscle; a few fuse with the descending branch to the omohyoid, and are to that extent accessory. Aberrant and accessory branches arise because of failure to fuse or to remain fused with other phrenic fibers. Aberrant twigs usually lie quite parallel to the main phrenic trunk, some barely separated from it; others are more remote, and may lie anterior, lateral or medial to the trunk. They may continue as separate nerves to the diaphragm or may fuse with the main trunk at different levels, thus forming loops which sometimes include other structures, e. g., the thoracic duct of subclavian vein. Accessory branches join the nerve to the subclavius muscle or the ansa hypoglossi, then leave them to continue downward either as separate branches to the diaphragm or to fuse with the main phrenic trunk within the chest. Fibers of sympathetic nerves that transmit tonic impulses to the muscles of the diaphragm may join the phrenic nerves in their upper or lower cervical or intrathoracic portions or may reach the diaphragm independently.

Experimental studies and about 300 operations performed on human beings have led to a development of methods that satisfy the following requirements:

An incision that will offer a direct approach to the lower anterior surface of the scalenus antious muscle on or near which the main trunk of the phrenic nerve will be found.

Subcutaneous dissection that will provide adequate exposure safely and simply and permit of closure that leads uniformly to good healing without interference with function and with an insignificant scar.

Means to determine during operation when all the fibers that transmit motor impulses have been blocked and complete paralysis has been induced because, as already stated, aberrant and accessory branches are more often present than absent, but infrequently contain motor fibers. Consequently, the wider dissections needed to discover and to block them are usually futile and are more or less harmful as the branches transmit useful impulses.

Means to determine during operation when the fibers that transmit tonic impulses have been so effectively blocked that the upward displacement of the diaphragm may suffice to provide the most beneficial diminution in lung volume and restriction of its excursions.

Measures by which the transmission of all motor impulses may be interrupted for a few days, weeks or months or permanently.

OPERATIVE TECHNIC

The operation is performed with the patient under local anesthesia (1 per cent procaine hydrochloride), and lying on a fluoroscope table. Ten grains (0.65 Gm.) of sodium barbital given an hour before operation to eliminate the slight risk of poisoning from the anesthesia and to limit apprehension. If the left phrenic nerve

is to be blocked and exeresis is a possibility, the patients are given a glass of cream a half hour previously so that if the thoracic duct is torn, the discharge of chyle is immediately obvious, and ligation of the duct is facilitated.

If the left nerve is to be blocked and the lower left side of the chest is so dense that the diaphragm cannot be recognized fluoroscopically, patients are given carbonated water to create a contrast gas bubble in the cardia of the stomach.

A transverse incision is made in a skin crease just above the clavicle. It extends from 1 inch lateral to the outer margin of the sternomastoid muscle inward 1 or 2 inches mesial to that margin and exposes the anterior surface of the muscle. The superior lip is freed and retracted upward; fibers of the muscle are separated and retracted laterally, exposing the deep fascia (fig. 3).

Palpation locates the scalenus anticus muscle, and this determines the approach. In some persons the internal jugular vein overlies the muscle; in others, the

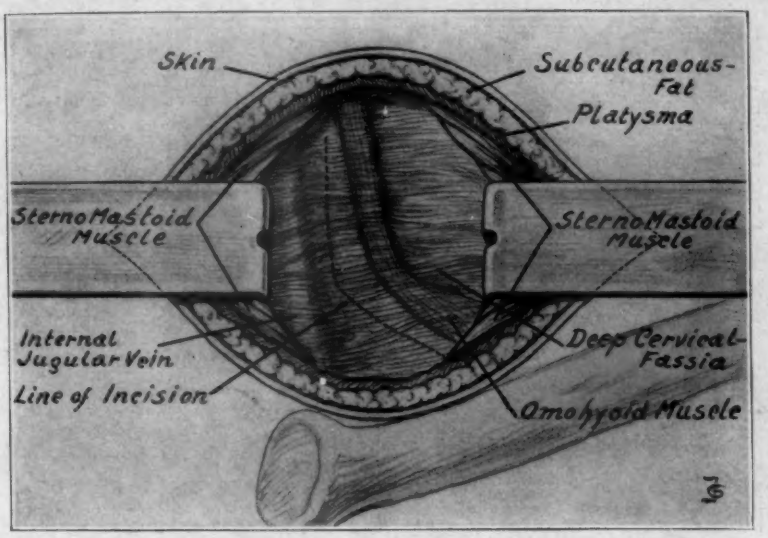

Fig. 3.—Dissection carried down to first layer of deep cervical fascia; sternomastoid split and retracted mesially and laterally.

muscle is lateral to the vein. If the vein overlies the muscle, its lateral border is exposed [4] and the vein is retracted mesially (fig. 4); otherwise it is not disturbed. The deep fascia is divided close to the mesio-inferior border of the omohyoid. The muscle is retracted laterally and the fascia mesially (fig. 3), exposing the layer of fat in front of the scalenus anticus muscle. Within this fat lies the transverse cervical artery and lymph glands, which may be considerably enlarged in patients suffering from pulmonary tuberculosis affecting the upper lobes. Blunt dissection, usually quite painless, makes it possible to expose the prevertebral fascia overlying the scalenus anticus muscle to which the phrenic nerve is usually attached without injuring the transverse cervical artery. It is

4. Care must be taken to see the lateral wall of the vein, which may be collapsed, before incising adjacent structures. Serious, even fatal, hemorrhages, and air embolism have been caused by failure to take this precaution.

desirable not to infiltrate the fat with procaine hydrochloride, as this may desensitize aberrant fibers. Rarely the lymphomas are so large and numerous that some of them must be excised to obtain exposure of the prevertebral fascia.

Lateral retraction of the margins of the aperture in the layer of deep fat permits identification of the main trunk of the phrenic which is freed by incising the fascia along its margins. A loop of thread is passed around the nerve and used as an elevator. If a transient paralysis is indicated, a few drops of 1 per cent cocaine are injected intraneurally. Fluoroscopic examination reveals whether or not the diaphragm is adequately paralyzed. If not, aberrant or accessory branches containing motor fibers are found and infiltrated or slightly crushed. Usually temporary or permanent paralysis is desired. The nerve is held loosely between the blades of a sharp hemostatic forceps, the lights are extinguished, the x-rays generated and the diaphragm visualized. Closing the clamp abruptly causes

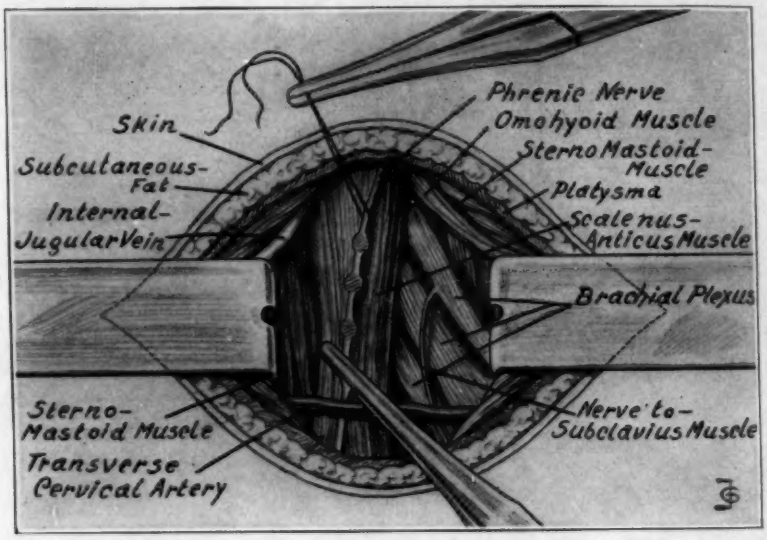

Fig. 4.—Dissection completed and nerve crushed. The incision and retraction shown is greater than that employed but is shown here to give the anatomic relations of adjacent structures.

an immediate contraction of the muscle, followed by relaxation and displacement upward. If all motor fibers have been blocked, the contour of the diaphragm is rounded and immobile save for the traction exerted by the other half of the diaphragm at the end of deep inspiration. If not, wavy undulations appear during inspiration produced by contraction of the unparalyzed fibers. Then it is necessary to locate aberrant and accessory branches and to repeat the crushing until the paralysis, as shown by the fluoroscope, is complete. Motor fibers are more commonly transmitted through aberrant than accessory branches, and if present in the accessory branches are more often in the nerve to the subclavius muscle than in the nerve to the omohyoid. The reason for not infiltrating the deep fat with procaine hydrochloride now becomes apparent.

The main trunk of the phrenic nerve contains both motor and sensory fibers, and when irritated it produces pain referred to the back of the shoulder or neck.

It sometimes lies in anomalous positions and can be identified by the pain caused if it is pinched. So, too, the aberrant and accessory branches may contain both motor and sensory fibers, though they may contain neither. Aberrant twigs are often so small that identification is difficult, but the pain produced by pinching frequently is helpful in identifying them. Similarly, the provocation of pain makes the identification of the nerve to the subclavius easier. Occasionally it is necessary to crush all of the deep fat adjacent to the aperture to induce complete paralysis.

When the transmission of the tonic impulses is blocked effectively, the diaphragm is not only displaced to a higher level which would not of itself be recognizable, but it is also rendered so atonic that a paradox appears. The paralyzed side rises during inspiration. A paradox appears immediately or after a few days in a majority of those in whom the induced paralysis is complete. It is as yet uncertain whether there is any material difference in the benefits conferred between complete paralysis with and without effective atonicity.[5]

Once the nerve or nerves that contain fibers which transmit all motor impulses to the diaphragm have been identified, it is possible to induce temporary paralysis of approximately desired duration (phrenemphraxis). Crushing nerves moderately severely in two places will be effective for eight or ten weeks; crushing them severely in four places will protract paralysis for three or four months. More severe crushing in five places will induce paralysis of longer duration, but recovery is uncertain; either the nerve fibers do not regenerate, or the degeneration in the muscle cells is irrecoverable. It now seems likely that when preliminary crushing induces a paradox, the total crushing should be less severe to avoid the degeneration that imposes permanent paralysis.

Permanent paralysis is induced either by resection of an inch or more (phrenisectomy) of nerves containing motor fibers or by the division of such nerves and extraction of their distal portions (exeresis). Phrenisectomy is preferable when the paralysis induced by crushing is complete and the atonicity is judged to be adequate. Pain is limited to the first crushing, and there is no danger. When the paralysis caused by crushing is incomplete or the atonicity is inadequate, the main trunk of the phrenic is divided and the distal portion gradually withdrawn. Extraction is painful if there are dense pleuritic adhesions; it is not always efficacious, and is not without danger. Intrathoracic hemorrhages have been reported. It is stated that a subclavian vein was torn, and a fatal hemorrhage resulted. We have noted tearing of the thoracic duct during the extraction of two left phrenic nerves. Both were ligated without producing symptoms. In one patient exeresis failed to induce complete paralysis. An aberrant or accessory branch which escaped detection extended independently to the diaphragm, or some motor impulses were delivered through fibers in the twelfth thoracic nerve. Moreover, exeresis

5. The degree of pulmonary deflation approaches more closely the status of collapse if atonicity is effective and intravascular peripheral resistance is reduced to the limit of possibility, and probably the excursions of the ribs are minimized so that dissemination is restricted to the utmost unless the lung is immobolized. Complete immobilization of the lung automatically reduces unwholesomely the amount of blood delivered through the bronchial arteries which, unlike the pulmonary vessels, are under vasomotor control. It also introduces the atrophy of nonuse and curtails the activities of tissue cells. Bronchial arterial blood furnishes the lungs and visceral pleura in human beings with the bulk of nutrition and of the cellular and noncellular elements which contribute the major portion of resistance, defense and repair.

will not induce effective atonicity manifest in paradoxic inspiration when the fibers of the sympathetic nerves that transmit tonic impulses reach the diaphragm independently or unite with the phrenic below the level at which it tears.

Closure.—The margins of the aperture made in the deep fat by blunt dissection are approximated with a pursestring suture of fine catgut. The deep fascia and the fibers of the sternomastoid muscle are united with interrupted stitches. The subcutaneous fat and the platysma muscle are united with interrupted catgut stitches so placed that when tied the knots are buried deeply after the margins of cleavage in the sternomastoid have been sutured loosely. The skin is closed accurately with fine silk stitches (fig. 5). When the hemostasis has been complete, if the skin stitches are removed on the second day and approximation maintained with strips of adhesive plaster, the healing is excellent and keloids exceptional.

Postoperative Care.—Robust patients should remain in bed for three days to avoid tachycardia while the intrapulmonary circulation is becoming readjusted.

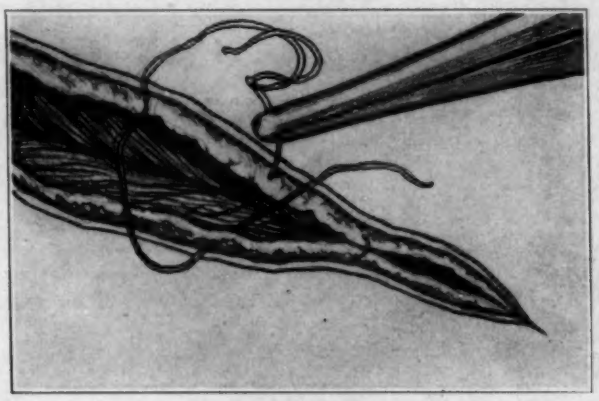

Fig. 5.—Closure of subcutaneous fat and platysma.

Ill patients with advanced pulmonary lesions often suffer from tachycardia, increased cough and expectoration during this interval and need absolute rest.

THERAPEUTIC ASPECTS

Clinical and experimental evidence suffices to explain and to prove the utility of induced paralysis, to define the states that make it futile, to indicate certain conditions in which it has not been but should be employed, and to disclose its disadvantages.[6]

6. Reduction in lung volume (partial deflation) and limitation of excursions not only increase pleuropulmonary powers of resistance, defense and repair, and restrict dissemination from lesions, but also the reduction in intrapleural negative pressures permits the walls of cavities in the parenchyma to collapse and facilitates the contractions of the wall of dilated bronchi. Alterations in intrapulmonary circulation which are favorable to patients who retain hematopoietic capacity and myocardial competence are futile in other patients whose blood-forming powers are irreparably impaired, whose heart muscle is exhausted or whose lesions are

Utility.—The sooner paralysis is induced, the larger the element of prophylaxis and the greater the benefits. A summary of personal observations and experiences follows.

Empyema.—Acute: Induced paralysis is applicable only to interlobar and supradiaphragmatic forms, as spontaneous paralysis occurs when the diaphragm is involved. Temporary unilateral paralysis is then beneficial whether open or closed drainage is employed.

Chronic: This type occurs in two forms, tuberculous and nontuberculous. Permanent unilateral paralysis is beneficial when the diaphragm is not already immobilized reflexly or by dense adhesions. It limits the extent of subsequent thoracoplasty, if that is needed to promote healing.

Abscess of the Lung.—Acute and Single: Temporary unilateral paralysis is beneficial when the abscess does not communicate with bronchi and postural drainage is impossible. It may obviate the necessity for external drainage.

Chronic, Single or Multiple, Actinomycosis and Tuberculosis: Permanent unilateral paralysis is beneficial if patients have not lost their capacity to make blood, or the myocardium is not too weakened. It prolongs life and reduces the extent of subsequent thoracoplasty needed to promote healing.

Pleuropulmonary Abscess.—Gangrenous: Permanent unilateral paralysis, if the abscess is large, or temporary paralysis if it is limited, hastens reduction of the cavity and lessens or eliminates subsequent thoracoplasty.

Bronchiectasis.—Incipient: Temporary unilateral paralysis together with other measures, including postural drainage, may introduce recovery.

Moderately Advanced: Permanent unilateral paralysis may, if other measures are employed, lead to sufficient improvement to be satisfactory. If not, wide, extrapleural resection of the lower ribs will introduce recovery.

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prohibitively advanced. Incipient or impending, e. g., traumatic and operative, pleuropulmonary inflammations unaccompanied by paresis of the diaphragm occurring in less robust persons, particularly if there is myocardial weakness, can be made least ominous, distressing and probably shortened if a transient or brief temporary paralysis is induced. Reduction of 10 per cent in vital capacity in a robust person in whom induced unilateral paralysis is seldom indicated would be revealed by unusual dyspnea and tachycardia only in extraordinary physical exertion. Reduction of vital capacity would exceed 10 per cent after induced unilateral paralysis in a person having pleuropulmonary lesions and usually a weakened myocardium. Indeed, the limitation in external respiration might be prohibitive of even restricted physical effort. Bilateral induced paralysis produces even in the robust a transient dyspnea that simulates the consequences of breathlessness resulting from thoracic injury.

Advanced: Permanent unilateral paralysis, wide resection of the lower six ribs and intercostal muscles and employment of other measures may produce satisfactory recovery. If not, the patients are prepared for the extrapleural lobectomy of Whittemore or the cautery lobectomy of Graham.

Pulmonary Tuberculosis.—Incipient: Whether the disease is of the adult or infantile forms, temporary induced unilateral paralysis employed in conjunction with other measures, including proper exposures to sunshine and, when indicated, supplemented with transfusions of unmodified blood, promotes the most certain and rapid convalescence. Our experience indicates that this procedure, if employed immediately after diagnosis is made, will materially reduce the duration and extent of disability.

Moderately Advanced: All measures are futile if the patients are highly susceptible, i. e., have lost hematopoietic capacity, which can be determined by blood counts and estimations of sedimentation rates repeated during an interval of several weeks while they are being given appropriate treatment, including transfusions of blood. Other patients who retain or can regain their blood-forming powers are benefited greatly by unilateral temporary or permanent paralysis. The healing of their lesions may suffice to obviate the need of thoracoplasty, or, if not, to restrict the number of ribs that must be resected to permit of such healing. Sometimes a temporary paralysis must be made permanent if after the diaphragm regains activity the signs and symptoms indicate reawakening of the disease.

Advanced: A larger proportion of patients in this group have lost blood-forming capacity than in the preceding. Others have irreparable myocardial incompetence; still others have irreparably advanced lesions, often bilateral. The balance can be benefited by permanent unilateral paralysis followed by more or less extensive thoracoplasty, particularly if bolstered by multiple transfusions. Some can be enabled to enter gainful occupations. In a few, it is said, a temporary paralysis of the opposite side of the diaphragm may be helpful.

Hemoptysis.—Hemorrhages (bright blood) from bronchial arteries are little affected by paralysis of the diaphragm. Hemorrhages from the pulmonary artery, in which the pressure is about one sixth of the systemic arteries, are usually promptly, and as a rule permanently, controlled.

Preparation for Thoracotomy.—Emergency: Emergency thoracotomies are performed to relieve injuries associated with hemothorax or hemopneumothorax and to relieve strangulated diaphragmatic hernia often resulting from trauma.

Hemothorax produces paresis of the diaphragm within an hour or two; later it becomes a paralysis. If when the chest is opened at the site of election (fifth rib) the diaphragm begins to contract, a transient paralysis (four days) should be induced by injecting 1 per cent cocaine into the phrenic nerve, which is easily reached in the portion that lies on the pericardium. Should the chest be opened at a lower level, particularly when there is no hemothorax, it is safest to induce temporary paralysis by a cervical phrenemphraxis half an hour or more before thoracotomy.

Thoracotomies, performed to repair unstrangulated diaphragmatic hernia, to remove intrathoracic cysts and neoplasms, for exploration or to remove extensive tumors of the wall of the chest should be preceded two or more days by temporary paralysis if after healing the lung can regain its normal volume, or by permanent paralysis if there is to be a reduction in the volume of the lung that will exceed the amount compensatory emphysema can correct.

The reasons are definite. An immobile diaphragm facilitates operation. Reduced volume and excursions of the lung and the consequent increment in unit volumes of blood raise pleuropulmonary resistance to infection several-fold, promote repair and reduce discomforts.

Wider Application.—Induced transient paralysis has not been employed in combating severe types of traumatic pleuritis, particularly when accompanied by effusion. Induced temporary paralysis has not been utilized in the treatment for pneumonias of the central type, whether bronchial or lobar, which do not provoke sufficient irritation of the visceral pleura to cause reflex inactivation of the diaphragm nor in the treatment for unresolved pneumonia or of incipient pneumonic pleuritis when the diaphragm is not immobile.

Benefits to be obtained under such conditions are not hypothetical, but proved, and exceed the slight discomforts of a simple operation and the temporary reduction in vital capacity which, if it is embarrassing, can be overcome by placing the patients in an oxygen chamber.

SUMMARY

Means are available to induce, safely and with little discomfort, transient, temporary or permanent unilateral or bilateral paralyses of the diaphragm which reproduce spontaneous paralyses that are natural protective responses to the more acute pleuropulmonary irritations.

The consequences of the paralysis are both beneficial and detrimental and have been proved experimentally and clinically. The benefits are an increment in pleuropulmonary powers of resistance, defense and repair and in the restriction of dissemination of noxious products, bacteria and tumor cells from inflammatory and neoplastic lesions.

The detriments, a reduction in vital capacity, often little, if at all, beyond that imposed by disease, need only be transient or temporary unless permanent benefits exceed permanent detriments.

The earlier paralysis is induced, the greater its immediate and prophylactic value.

Temporary paralysis (phrenemphraxis) should not be induced if transient paralysis will suffice.

Permanent paralysis (phrenisectomy, exersis) should be induced only if temporary paralysis has been proved to be inefficacious or would be insufficient to meet requirements.

CONCLUSIONS

Induced paralysis of the diaphragm is beneficial to patients suffering from a number of pleuropulmonary diseases.

It makes thoracotomy and thoracoplasty simpler and safer.

Its greatest value, prophylaxis, is attained by early utilization.

Experimental and clinical evidence indicates a more frequent, more extended and earlier employment of this minor procedure, but always in conjunction with other measures.

EXPERIMENTAL HEALING OF BONE AFTER PARATHYROIDECTOMY *

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AND
DEAN L. RIDER, M.D.
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As a part of a problem in healing of bone under varying conditions of abnormal blood calcium and phosphorus undertaken by the senior author, the definite results of experimental healing of bone in dogs after parathyroidectomy seem worthy of a separate report.

One of the first experiments on the influence of the parathyroids on healing of bone was made by Morel [1] in 1910; this covered the influence of the parathyroids on consolidation of fractured bones in cats, and followed his report of the previous year, which dealt with the action of the parathyroids on the growth of healthy bone. His experiments covered, first, ablation of most of the parathyroid tissue in adult cats, which was found not to retard the process of ossification of experimental fractures; second, similar ablation of most of the parathyroid and thyroid tissue in young cats, which resulted in a delay in the healing of the fractures for an average of seven weeks. Four cats were used: two died; one had tetany, and in the fourth a delayed bony union was demonstrated in comparison with two controls that showed normal union after fracture. The process in the thyroparathyroidectomized cats was characterized by a flexible voluminous callus which was almost exclusively cartilaginous. Morel referred to Canal's work and asserted that his conclusions verified Canal's; namely, that this operation in cats caused a retardation of bony healing after fracture in young cats only, not in adults. After study of this report, the feeling exists that a complete thyroparathyroidectomy was not done on the animals that lived, but that enough parathyroid tissue was removed to verify delayed union after fracture in cats.

The influence of parathyroidectomy on bony healing in rats and puppies was investigated by Ogawa, in 1925, from a different angle.[2]

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* From the Surgical Department, Rush Medical College.

1. Morel, L.: Compt. rend. Soc. de biol. **68**:163, 1910; **66**:837, 1909.

2. Ogawa: Healing of Fractures in Reference to the Parathyroids, Arch. exper. Path. u. Pharmakol. **109**:83, 1925.

He carefully reviewed the literature back to 1896 and believed that the difference in results obtained in these experiments was due to improper removal of the parathyroids, that is, incomplete removal, some of the active glandular tissue remaining. After parathyroidectomy on his animals, he gaged the effect on healing of bone by a chemical analysis

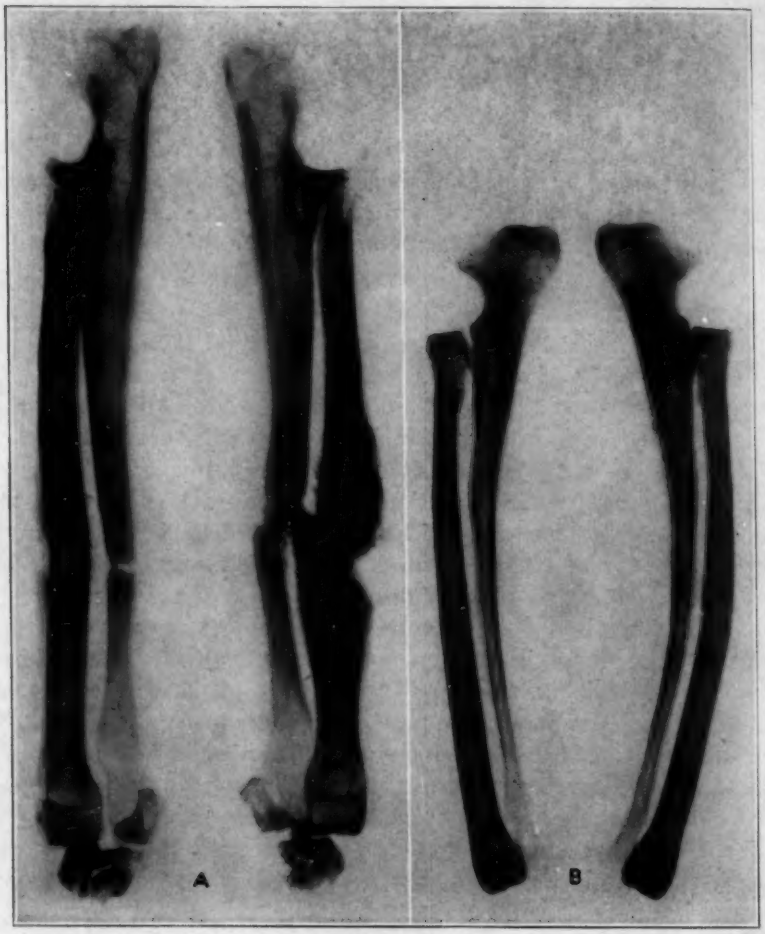

Fig. 1.—*A*, bones removed from the legs of dog 50, left and right. See table 3. The right leg is shown six weeks after fracture; it has reasonable bony union. The left leg is shown three weeks after fracture; it presents no union, especially in the radius. Considerable amount of callus is formed beneath the periosteum extending up the shaft of both bones of both legs, and yet the amount of callus in the fracture is slight. *B*, bones from the legs of dog 51 (table 3). Only the right leg of this dog was broken, and three weeks have elapsed since the fracture. The scant amount of callus attempt is apparent, although the bones are in excellent apposition. No union is present.

of the callus, estimating its calcium content (CaO_2). He found that if parathyroid extract was given to the animal after experimental fracture, the callus was greater than in normal controls; that is, it contained less water, more ash and more calcium. After thyroidectomy alone there was also a greater amount of callus, with no change in the water and ash content, but a slightly greater amount of calcium than in normal controls. He observed that in dogs it was necessary to remove the thyroid also, in order to be sure that all parathyroid tissue was obtained. The conclusion was reached that the parathyroid hormone and the thyroid hormone work antagonistically in the laying down of calcium in callus.

Another interesting series of experiments was performed by Hammett,[3] in whose papers are given the results of a study of the gross anatomy and chemical differentiation of the humerus and femur of the male and female albino rat during their period of growth, from 75 to 150 days of age, and the influence of thyroparathyroidectomy and parathyroidectomy on this growth. The study concerned itself mostly with an ash analysis of the bones with determination of the calcium, magnesium and phosphorus contents. The glandular deficiencies were initiated at 75 days of age.

It was found that in normal bone at 75 days of age the calcium percentage content of the femur is less than that of the humerus in both sexes; there is no discussable difference in the magnesium or the phosphorus contents. During the period from 75 to 100 days of age, there is a definite increase in the calcium percentage of both bones of both sexes, but no shifts in the magnesium or phosphorus percentages. This age difference is directly correlatable with the fact that the rate of growth of the femur in weight and length and in increment of water, organic matter and ash, are greater than that of the humerus during the growth period from 75 to 100 days of age.

The bones of thyroparathyroidectomized rats showed that the percentage of composition of these bones, femur and humerus, was the same, save that in males the phosphorus percentage was greater in the femur than in the humerus. Both these bones of both sexes of the group operated on had less ash, calcium, magnesium and phosphorus. The bones were also lighter and shorter, and contained less water and organic matter. The bone of both sexes of parathyroidectomized rats contained smaller absolute amounts of ash, calcium and phosphorus.

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3. Hammett, F. S.: Thyro-parathyroidectomy, J. Metab. Research **5**:169 (April-June) 1924; Calcium, Magnesium and Phosphorus Content in Bone Ash of Rats, J. Biol. Chem. **72**:505 (April) 1927; Chemical Differentiation of Bone During Growth Studies of Thyroid Apparatus, J. Exper. Biol. **47**:95 (Feb.) 1927.

In 1927, Stewart and Percival,[4] in their studies of calcium metabolism, especially that on the action of the parathyroid glands in controlling the concentration of the calcium in the blood, observed that the parathyroids may affect the absorption or excretion of calcium or at least exert some controlling action on the equilibrium between the different forms of combination in which calcium exists in the blood and between the concentration in the blood and in the tissues. It was Green-

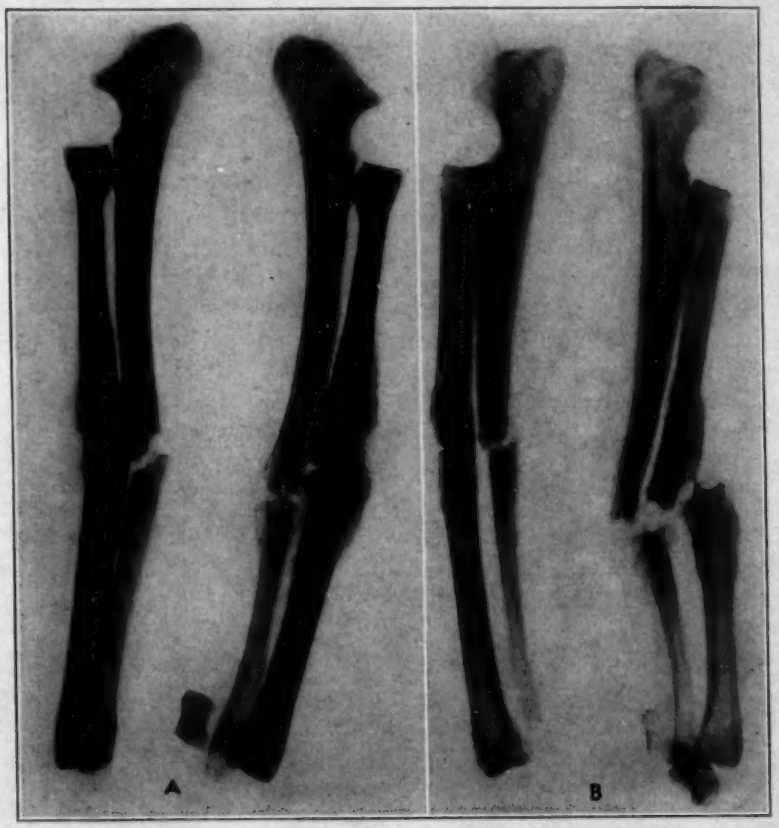

Fig. 2.—*A*, bones from the legs of dog 53 (table 3). The right leg is shown six weeks, and the left leg, three weeks after fracture. Apposition between the fragments in these fractures is not as complete as in the legs of dogs 50 and 51. There is a scant amount of callus at the site of fracture, even in the six weeks' fracture of the right leg; the left leg, three weeks after fracture, shows little callus. Incomplete union is seen in both legs. *B*, bones from the legs of dog 52, the right leg six weeks, and the left three weeks, after fracture. Apposition in the right leg is not as good as in the left leg. There is insufficient amount of callus at the site of fracture, so that nonunion is apparent in both specimens. There is still considerable subperiosteal callus remote from the site of fracture.

4. Stewart, C. P., and Percival, G. H.: Studies in Calcium Metabolism, Biochem. J. **21**:301, 1927.

wald and Gross who suggested, in 1925, that the parathyroid hormone is the substance which keeps in solution the large excess of basic calcium phosphate.

Stewart and Percival [4] found that in cats repeated hemorrhages (bleedings) did not reduce the proportion of blood calcium. Parathyroid hormone given subcutaneously caused a rise in blood calcium about one-half as fast in cats as in dogs. When it was given intravenously, the action was much quicker. Oral administration of sodium bicarbonate lowered blood calcium, probably by producing a decreased acidity of the intestinal contents, which militates against the absorption of calcium, or by bringing about an increased absorption of sodium, thereby causing an alkalosis, which results in a direct lowering of blood calcium. Their experiments show that the parathyroid hormone exerts an influence on the blood calcium content without drawing on external sources of calcium, that is, without stimulating absorption of calcium from the alimentary tract. The increase in serum calcium following the administration of parathyroid hormone is due, then, to the withdrawal of calcium from body tissues, as the increase takes place without any diminution in the excretion of calcium and without possibility of any additional absorption from the alimentary tract.

In efforts to ward off parathyroid tetany, Wade,[5] in 1929, gave animals cod liver oil in amounts up to 50 cc. daily for two to three weeks before parathyroidectomy, and he found that while fatal tetany was delayed and the general severity of the tetany was diminished, the blood calcium dropped as much as or even lower than in animals that had not had cod liver oil.

In 1928, Fine and Brown [6] studied the influence of parathyroid extract-Collip [7] on regeneration of bone. They worked with dogs in an effort to study repair of bone under the influence of the extract. They made trephine openings in the femur and found no evidence of difference in regeneration of the bones compared with controls, either in examination by means of the x-rays or in the gross specimen. They also removed ribs subperiosteally, isolating the dogs on a meat and milk diet, and concluded that the parathyroid extract-Collip delayed the speed of deposition of calcium in regenerating bones of young dogs; its action

5. Wade, P. A.: Calcium and Cholesterol in Relation to Thyroid Parathyroid Apparatus, Am. J. M. Sc. **177**:79 (June) 1929.

6. Fine and Brown: Influence of Parathormone on Bone Regenerations, New England J. Med. **198**:932 (June 21) 1928.

7. Collip, J. B.: Therapeutic Value of Parathormone, J. A. M. A. **87**:908 (Sept. 18) 1926; Parathyroid Hormone, J. Biol. Chem. **63**:395 (March) 1925; Calcium Mobilizing Hormone of Parathyroid Glands, J. A. M. A. **88**:565 (Feb. 19) 1927.

on adult dogs was not ascertained. They believed, consequently, that the use of the extract for delayed bony union was not based on any sound principle.

The healing of fracture in parathyroidectomized albino rats was also investigated by Chandler,[8] who caused a fracture of one bone of the forelimb at the time of parathyroidectomy. Histologic studies of the bones ten, fourteen and twenty-one days after operation were made.

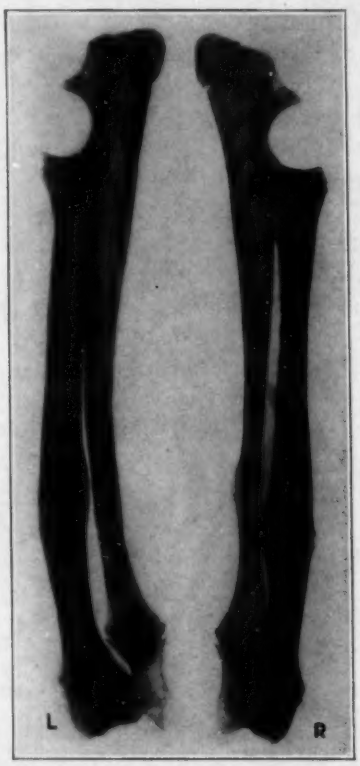

Fig. 3.—Bones removed from the legs of an average normal control dog (table 3). The right leg, shown six weeks after fracture, presents firm bony union with solidified callus. The left leg shows a satisfactory bony union with firm callus formation. This represents a normal reaction of a normal dog to such experimental fracture.

Litter mates were used as controls. There was no significant difference in the healing of the bones in the two groups of albino rats.

A clinical assumption after observation on man, that injection of parathyroid extract increases the calcium in the blood, thereby furnishing

8. Chandler, S. B.: The Healing of Fractures in Parathyroidectomized Albino Rats, Anat. Rec. **35**:7, 1927.

more calcium for fracture callus has rightly been questioned. Union following administration of the parathyroid extract-Collip in instances of delayed union is not necessarily caused by the injection. Lehman and Cole [9] believed that the issue has been confused, that the action of the parathyroid extract is to mobilize the fixed calcium of the body and that hence it should not offer aid in hastening or inducing a deposit of calcium salts in the soft tissue (callus) about a fracture. They believed that excess callus found after using the parathyroid extract must come largely from the bones themselves. Hunter and Aub, in their study of lead poisoning, found that calcium excretion in patients is rapidly increased in an amount parallel to an increase in the blood serum calcium on the administration of parathyroid extract. If analogy is drawn then between the white rat and man, the level of the blood calcium is not the essential factor on which depends the rate of calcification of callus, as the tendency after injection of parathyroid extract is toward a reduction of the calcium in the bones, and one would expect the withdrawal of calcium from the callus itself and a delay of union.

As a logical sequence to such an argument, Gold [10] discussed the significance of enlargement of the parathyroid gland in osteitis fibrosa generalisata. He found that the literature on this disease, Paget's disease and osteomalacia often mentioned associated parathyroid enlargement. Of seventeen cases of parathyroid enlargement studied at autopsy by Maresch of Vienna, thirteen gave evidence of skeletal changes. In six instances in this group, osteomalacia had been diagnosed; in five, osteitis fibrosa; in one, osteoporosis, and in one, Paget's disease.

Gold reported the case of a woman, aged 54, who had osteitis fibrosa cystica. A tumor of the right superior parathyroid was found and extirpated. Six months after operation there was improvement clinically, chemically and roentgenologically. The blood calcium dropped from 30 per cent plus to normal. The previous abnormal excretion of calcium in the urine also approached normal. Microscopic examination of the gland showed a benign adenoma.

Ross [11] said that he had repeated the experiments of Morel,[1] Ogawa [2] and others, using improved precautions, in a study of the effects of excision of different amounts of the four parathyroid glands in cats. He verified the condition of the experimental fractures at different intervals by roentgenologic examination and determined the blood calcium content during this course of time.

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9. Lehman, E. P., and Cole, W. H.: Parathyroid Hormone and Calcification, J. A. M. A. **89**:587 (Aug. 20) 1927.

10. Gold, Ernst: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **41**:63, 1928.

11. Ross, D. E.: Relation of the Parathyroids to the Healing of a Fracture as Controlled by the Roentgen Rays, Arch. Surg. **16**:922 (April) 1928.

The phosphorus content of the blood was determined both before and after the removal of two or three parathyroid glands, but no change in the phosphorus level was found. In the first five or six days following fracture in a normal cat, an invasion of the blood clot at the site of fracture by fibrous connective tissue was found. By the tenth or eleventh day, the blood clot had almost entirely disappeared and was replaced by connective tissue, with a small amount of cartilage and a

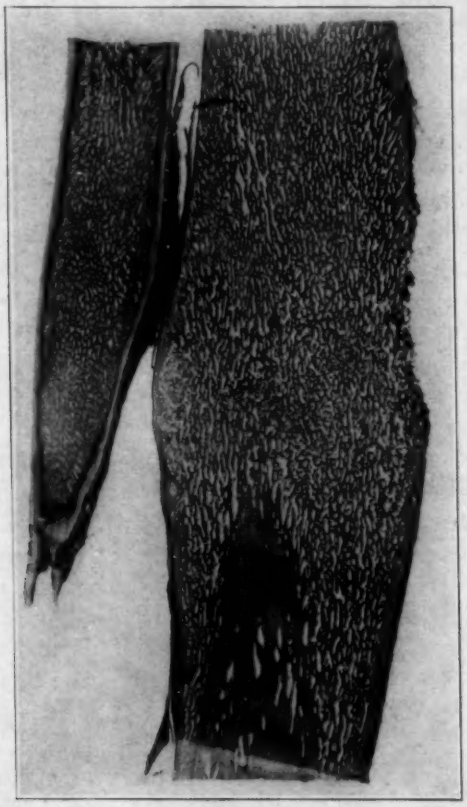

Fig. 4.—Photomicrograph of the right leg of an average normal dog six weeks after fracture; × 3.66. See table 4. There is abundant callus with calcified bony trabeculae almost hiding the site of the fracture. The medullary cavity is not yet established through the site of fracture.

few small areas of bone. This invasion of blood clot by connective tissue and the formation of cartilage occur in cats from which three parathyroids have been removed. The process of bony union after that stage is delayed. Ross concluded that removal of two parathyroids does not (in cats) delay union of a fracture; removal of three parathyroids

delays union for as long as from four to five weeks. The excision of two parathyroids does not diminish the blood calcium, but excision of three causes a drop of from 2 to 3 mg. of serum calcium per hundred cubic centimeters. When the blood calcium returns to a normal level, bony union of these experimental fractures follows. Removal of two or three parathyroids does not influence the blood phosphorus level, and a certain amount of mobility at the site of fracture is not deleterious to bony union.

In the experiments on dogs here reported, Scholz' dictum that the untreated cretin retains phosphorus and excretes an abnormal amount of alkaline earths was borne in mind, and thyroid was given to the thyroparathyroidectomized dogs in doses of 3 grains (0.18 Gm.) per diem, because it was felt that the administration of this thyroid exerted no influence on the phosphorus metabolism, but reduced the urinary excretion of alkaline earths, particularly calcium, and thereby influenced tetany favorably. A confirmation of this fact was noted by Aub, Bauer, Heath and Ropes, who noticed that the increase of calcium excretion in exophthalmic goiter is out of proportion to the basal metabolism; e. g., a basal metabolic rate of 55 plus gave a calcium excretion of 170 per cent above normal. Similarly, in six patients with myxedema it was found by them that the average excretion of calcium was 40 per cent below normal. Without any change in dietary intake, feeding thyroid to these patients resulted in an increase in both metabolism and calcium excretion, verifying the point that the thyroid extract acts to increase the endogenous calcium metabolism while the extra elimination of calcium comes from the tissues, presumably mostly from the bones. In two instances of parathyroid tetany with low calcium levels in both blood and excreta, the response to thyroid therapy was shown by a distinct elevation not only of the calcium excretion but also of the serum level. Aub, Bauer, Heath and Ropes considered that the effect of thyroid secretion on calcium excretion is greater than its effect on total metabolism. Probably the effect of thyroid is merely a direct catabolic action on the calcium deposits in the bones, although the high rate of calcium elimination is not found in the blood itself.

This reserve or easily influenced supply of calcium may be in cancellous bone. Bauer, Aub and Albright [12] noted that the amount of cancellous bone varies in different animals, and they concluded after their studies that the bone trabeculae of cancellous bone are early depleted by prolonged administration of parathyroid extract-Collip; that a long-continued high calcium diet results in a rapid accumulation of

12. Bauer; Aub, and Albright: Calcium and Phosphorus Metabolism; Bone Trabeculae as Source of Calcium, J. Exper. Med. **49**:145 (Jan. 10) 1929; Quart. J. Med. **20**:123, 1926-1927.

trabeculae and that bone trabeculae serve as a storehouse of readily available calcium, whereas the shafts of bones undergo a slow progressive exchange of inorganic salts and are not influenced, except in case of unusual body demands.

One theory might be advanced in the consideration of the physics of bone, namely, that the calcium in bones is divided into two parts, a

Fig. 5.—Photomicrograph of left leg of an average normal dog three weeks after fracture; × 3.66. The union is satisfactory, with calcified cartilage present and every evidence of bony union to follow. See table 4.

larger portion making up the solid structural part of the bone, which functions primarily as a mechanism for body support, and a smaller, less stable or more easily influenced portion lying in the trabeculae of cancellous bone and acting as a ready reserve for use when body requirements demand calcium salts. The anatomic situation of the trabeculae accords with this theory; the trabeculae are most numerous where the blood

Fig. 6.—Photomicrograph of right leg of dog 50 six weeks after fracture. This dog had had a thyroparathyroidectomy. In table 4, a description of this section is available. There is much uncalcified callus with connective tissue and fat cells, but no mature bone is present.

Fig. 7.—The left leg of dog 50 which had undergone a thyroparathyroidectomy. No mature bone is present and nonunion is still seen. Consult table 4 for more details.

supply is greatest. The delicate bone trabeculae in close relationship to the bone-marrow are well situated to receive calcium deposits in times of calcium excess and to give up calcium in times of need.

The results obtained from the experimental work on dogs are explained in tables 1, 2, 3 and 4.

Table 1 shows the average determinations of serum calcium and phosphorus per hundred cubic centimeters in adult dogs.

Table 2 shows the clinical course of four dogs which, out of ten, survived thyroparathyroidectomy and the subsequent tetany and other mishaps and were subjected to experimental fracture. All dogs were kept in separate cages, mostly in an isolated part of the laboratory, and

TABLE 1.—*Determinations of Blood Calcium and Phosphorus in Dogs After Parathyroidectomy*

Dog 50, on Which Thyroparathyroidectomy Was Performed, April 17, 1929*	Calcium, per 100 Cc.	Phosphorus, per 100 Cc.	Diet	Weight, Kg.
April 16, 1929	10.2	3.8	Normal	13.6
April 23, 1929	6.3	5.8	Normal	14.0
May 10, 1929	7.0	5.9	Normal	14.5
May 23, 1929	6.9	7.0	Normal	15.0
June 1, 1929	6.3	7.4	Normal	15.2
June 14, 1929	6.5	7.8	Normal	14.5
June 26, 1929	6.8	7.8	Normal	13.9
July 4, 1929	6.5	8.2	Normal	12.8
July 11, 1929	6.1	10.0	Normal	11.9
July 12, 1929	6.1	9.4	Normal	....
Twenty normal dogs averaged	10.1	6.0		

* All dogs conformed more or less exactly to dog 50 in respect to these observations.

watched for tetany. Only the most assiduous attention and quick efforts made it possible to bring four dogs through to the point of fracture. It was found that these dogs after recovery from tetany did not take ether well. The fractures were induced by a Thomas wrench, and the leg involved was immediately enclosed in a circular plaster dressing. These dressings had to be renewed in several instances, and there was some movement at the site of fracture or some weight bearing when the dog got up. Several normal dogs, some litter mates, were used as controls.

Table 3 shows the results of clinical and roentgenologic examinations for the evidence of bony union in the four thyroparathyroidectomized dogs subjected to fracture.

Table 4 shows the microscopic evidence of healing of bone in the fractured legs of these four dogs, compared with that in the average normal dog.

TABLE 2.—*Clinical History of Dogs Subjected to Fracture After Parathyroidectomy*

Dog	Operation	Postoperative Treatment	Fracture	Postfracture Course	Fracture	Postfracture Course	Death
50	4/17/29, thyroparathyroidectomy	Calcium lactate 1.5 grain per kilogram of weight per diem in 3 parts; discontinued, 5/18/29	5/23/29, right leg, under ether	Tetany; return to calcium 6/16/29; 3 grains thyroid daily; 6/17/29, attempted to walk	6/20/29, left leg, under ether	No tetany; depressed; calcium lactate no influence; 6/29/29, improved	7/11/29, in tetany autopsy no thyroparathyroid tissue
51	5/6/29, thyroparathyroidectomy	Calcium gluconate in vein; thyroid removed; calcium lactate by stomach tube; discontinued, 5/21/29	6/1/29, right leg, under ether	Thyroid feeding; depressed; 6/11/29, tetany; calcium lactate renewed	.....	.....	6/20/29, in tetany autopsy no thyroparathyroid tissue
53	6/8/29, thyroparathyroidectomy	Thyroid removed; calcium lactate, 6/10/29 to 6/18/29	6/20/29, right leg, under ether	Depressed; calcium lactate therapy no help; no attempt to use leg	7/13/29, left leg, under ether	Not much attempt to use legs as right not strong; few steps 7/27/29 to 8/1/29; on both legs	8/1/29, no thyroparathyroid tissue
52	6/14/29, thyroparathyroidectomy	Thyroid removed; calcium lactate, 6/17/29 to 6/24/29	6/27/29, right leg, under ether	Good condition; 7/2/29, attempted to use leg	7/18/29, left leg, under ether	Lay in cage; began to walk 8/1/29	8/8/29 killed; no thyroparathyroid tissue
Normal Control Dog (example of several dogs)							
	Normal dog; blood calcium 9.8-10.6; blood phosphate 5.2-6.4	No glandular operation; no medication	2/28/29, right leg, under ether	Not much weight on leg first week; seemed to have pain in it when walking until 3/18/29; then normal, no limp; cast off 3/20/29	3/21/29, left leg, under ether	Recovery slow; depressed 1 week; by 4/5/29 walking without limp	4/10/29, killed

TABLE 3.—*Results of Clinical and Roentgenologic Examination for Evidence of Healing of Bone in Dogs After Parathyroidectomy*

Dog	Clinical Examination		Examination by Means of X-Rays	
	Right Leg	Left Leg	Right Leg	Left Leg
50	At 6 weeks, bony union	At 3 weeks, small callus; motion at site of fracture	At 6 weeks, bony union	At 3 weeks, small callus; nonunion in radius
51	At 3 weeks, no union; motion between fragments	.....	At 3 weeks, little callus, fracture still looks recent	
53	At 6 weeks, callus apparent, especially in radius; crepitus when moved; union firm, except in lateral plane	At 3 weeks, callus apparent; some bending, slight motion in both bones	At 6 weeks, callus good, denser on radius; firm bony union; ulna less dense but more so than 3 weeks' specimen	At 3 weeks, fair callus both bones, greater in radius, which appears completely united; ulna, clear space between; incomplete union
52	At 6 weeks, callus apparent; false motion both bones; slight crepitus	At 3 weeks, callus around radius, little around ulna; false motion at site of fracture; no inclusion of soft parts	At 6 weeks, malapposition of fragments; apparent callus, especially in distal fragments; true nonunion; most of callus subperiosteal, not around fracture	At 3 weeks, apposition good; more callus around radius, subperiosteal, not in plane of fracture; no union present
Normal Control Dog (example of several dogs)				
	At 6 weeks, firm bony union	At 3 weeks, firm bony union	At 6 weeks, firm bony union	At 3 weeks, firm bony union

TABLE 4.—*Results of Microscopic Examination of Experimental Bone Healing After Parathyroidectomy*

	Three Weeks After Fracture	Six Weeks After Fracture
Dog 10 (normal control)	Abundant network of trabeculae along fracture plane; small islands of calcified cartilage surrounding small spicules of necrotic bone; islands surrounded by osteoid tissue; around periphery, partly calcified cellular tissue with large bone cells and some old hemorrhages	Abundant network calcified bony trabeculae fills cavity of bone-marrow and extends on outside of shaft for 20 mm.; thickness, 3 mm.; spaces between trabeculae filled by vascular cellular connective tissue
Dog 50 (parathyroid removed)	Much uncalcified callus, out of which develop branches trabeculae of osteoid tissue which surrounds poorly calcified islands of callus; in spaces between trabeculae are fibrillar connective tissue and fat cells; no mature bone	Irregular structureless masses of calcium salts arranged perpendicularly to surface of bone; these masses surrounded by uncalcified callus, formed of trabeculae; spaces between trabeculae contain connective tissue and fat
Dog 51 (parathyroid removed)	No newly formed tissue along fracture plane; on outside is bridge of small amount of callus surrounded by old blood; slender osteophytes about the intact bone; no bony union	
Dog 53 (parathyroid removed)	Callus tissue; smaller amount of osteoid tissue than in 3 week stage of dog 50	Histology identical with that of six week specimen of dog 50
Dog 52 (parathyroid removed)	Fracture bridged on outside by callus; no union in plane of fracture	Histology corresponds to that of same period of dog 50, except central deposits of calcium are less extensive; no bony union

CONCLUSIONS

A study of serum calcium alone in dogs would show merely the height of the calcium stream or balance; it would not give any indication as to the direction of its flow, whether into excretory channels or into the bones. On these parathyroidectomized dogs in which tetany was controlled by the use of calcium lactate and thyroid extract, no determinations of the calcium content of the excreta were made. The lack of calcification of the bones after experimental fracture, in conjunction with the low blood calcium, led to the inference that the calcium stream was directed away from the bones after parathyroidectomy, and that parathyroidectomy, either through this change of calcium stream or balance or through some still undiscovered factor, delays the healing of fracture in experimental dogs.

A COMPARISON OF THE EFFECTS OF HEMORRHAGE UNDER ETHER ANESTHESIA AND UNDER SPINAL ANESTHESIA*

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Owing to the frequent employment of spinal anesthesia in recent years, a clearer understanding of its effect on the general circulation seems important. Occasional deaths following its use have been unexplained. Recently, we had occasion to observe a patient who died following the termination of an operation under spinal anesthesia. During the operation approximately 250 cc. of blood was lost. As no other cause for the patient's death was found, it was believed that the hemorrhage probably was responsible for it. The loss of this amount of blood in an adult patient under ether anesthesia does not usually produce deleterious effects.

The purpose of the present study is to determine the effects of loss of blood under ether anesthesia and under spinal anesthesia.

METHODS

Dogs were used in all experiments. The blood pressure level was determined by placing in the carotid artery a cannula which was connected to a mercury manometer. The cardiac output was calculated from the Fick formula:

$$\frac{\text{Cc. oxygen consumed per minute}}{\text{Cc. oxygen taken up by 1 cc. of blood in passing through the lungs}} = \text{Cc. of blood passing through the lungs per minute}$$

The animals were bled from a cannula placed in either the femoral or the carotid artery.

In the experiments in which the effects of hemorrhage during ether anesthesia were determined, the animals were anesthetized by ether for periods of time varying from one hour and thirty-seven minutes to two hours and thirty-seven minutes before the initial bleeding. The anesthesia was profound in all instances. At the end of this period, the cardiac output and the blood pressure were determined. At five minute intervals, until the animal had been bled from three to six times in the different experiments, an amount of blood was removed at each bleeding which equaled in most instances 5 cc. per kilogram of body weight. Five minutes after the last removal of blood, the cardiac output and blood pressure were again determined, and the experiment was discontinued.

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In the experiments in which the effects of hemorrhage during spinal anesthesia were determined, barbital or morphine in amounts sufficient to permit the introduction of cannulas was given. A solution of procaine hydrochloride (1 per cent) and strychnine sulphate (0.1 per cent) was used in some experiments and procaine hydrochloride (1 per cent) in others. From 0.3 to 1 cc. of the fluid was injected into the spinal canal in the lumbar region. The animal was placed on its side for the introduction of the anesthetic and was then changed to the dorsal position. The board on which the animal was lying was at all times kept parallel to the floor. After the needle was introduced into the spinal canal, several drops of the spinal fluid were withdrawn into the syringe and reinjected with the procaine and strychnine sulphate solution. After periods of time varying from twenty to forty-seven minutes after the solution was injected, the cardiac output and blood pressure were determined. The blood was then removed from the animal usually at five minute intervals, the total amount removed varying in the different experiments from 8 to 30 cc. per kilogram. In most instances the individual bleedings were of approximately the same size as those in the experiments performed under ether anesthesia. After the last bleeding an attempt was again made to determine the cardiac output and blood pressure.

RESULTS

The cardiac output and blood pressure were not determined before the ether was administered. A comparison of the figures that were obtained after the animals had been anesthetized for varying intervals of time with those of similar figures on normal unanesthetized animals shows that the ether anesthesia did not alter markedly the cardiac output and blood pressure. Two of the four dogs were bled 0.5 per cent of the body weight at five minute intervals until 3 per cent had been removed. Determinations of the cardiac output and blood pressure after the last bleeding showed a marked decline as compared with that before the first bleeding but the animals were in no grave danger of immediate death. Removal of blood amounting to 1.5 per cent of the body weight caused some reduction in the cardiac output and blood pressure but spontaneous recovery of the animal undoubtedly would have taken place had the anesthetic been discontinued. The results of the experiments in which ether anesthesia was used are given in table 1.

In an attempt to determine whether or not ether anesthesia increases the danger of circulatory failure from hemorrhage, two animals were bled 0.5 per cent of the body weight at five minute intervals. No anesthetic was used except procaine hydrochloride which was injected at the site of the introduction of the cannula. The reaction of the animals to hemorrhage was approximately the same as that in the animals which were anesthetized by ether. As it has already been shown (Blalock and Harrison [1]) that normal dogs do not reach a state of severe shock until

1. Blalock, A., and Harrison, T. R.: The Regulation of Circulation: V. The Effect of Anemia and Hemorrhage on the Cardiac Output of Dogs, Am. J. Physiol. **80**:157, 1927.

TABLE 1.—*Effects of Hemorrhage During Ether Anesthesia*

Experiment	Weight, Kg.	Before Bleeding: Cardiac Output, Cc. per Minute	Before Bleeding: Mean Blood Pressure, Mm. of Mercury	After Last Bleeding: Cardiac Output, Cc. per Minute	After Last Bleeding: Mean Blood Pressure, Mm. of Mercury	Time Interval Between Beginning Anesthetic and Bleeding	Bled, Cc. per Kg.	Total Amount Bled, Cc. per Kg.
1	15.5	2,000	127	710	32	1 hr. 37 min. 1 hr. 42 min. 1 hr. 47 min. 1 hr. 52 min. 1 hr. 57 min. 2 hr. 2 min.	5 5 5 5 5 5	30
2	11.5	1,480	122	499	28	1 hr. 46 min. 1 hr. 51 min. 1 hr. 56 min. 2 hr. 1 min. 2 hr. 6 min. 2 hr. 11 min.	5 5 5 5 5 5	30
3	12.0	3,132	124	2,448	120	2 hr. 26 min. 2 hr. 31 min. 2 hr. 36 min.	5 5 5	15
4	11.3	2,456	105	1,235	50	2 hr. 37 min. 2 hr. 42 min. 2 hr. 47 min. 2 hr. 52 min.	4 4 4 4	16

TABLE 2.—*Effects of Hemorrhage During Spinal Anesthesia*

Experiment	Weight, Kg.	Before Bleeding: Cardiac Output, Cc. per Minute	Before Bleeding: Mean Blood Pressure, Mm. of Mercury	After Final Bleeding: Cardiac Output, Cc. per Minute	After Final Bleeding: Mean Blood Pressure, Mm. of Mercury	Time Interval Between Spinal Anesthetic and Bleeding	Bled, Cc. per Kg.	Total Amount Bled, Cc. per Kg.
1	10.0	420	34	0	0 (died)	25 minutes 30 minutes 35 minutes 40 minutes	4 4 4 4	16
2	12.3	800	84	0	0 (died)	25 minutes 30 minutes	4 4	8
3	13.6	660	46	0	0 (died)	40 minutes 50 minutes	4 4	8
4	11.8	1,340	66	420	28	45 minutes 40 minutes 45 minutes 50 minutes	4 4 4 4	16
5	9.0	2,530	95	450	40	25 minutes 30 minutes 35 minutes 40 minutes 45 minutes 50 minutes	5 5 5 5 5 5	30
6	11.4	2,100	70	365	16	20 minutes 25 minutes 30 minutes	5 5 5	15
7	13.6	2,230	66	0	0 (died)	13 minutes 25 minutes	6 6	12
8	16.8	2,540	110	1,010	82	47 min. 1 hr. 25 min. 1 hr. 55 min.	11 7 9	27
9	14.1	1,580	28	950	24	25 minutes	9	9

blood amounting to 3 or 4 per cent of the body weight has been removed, further observation on normal dogs seems unnecessary at the present time.

The effects of hemorrhage during spinal anesthesia were determined in nine experiments. The blood pressure and cardiac output before the initial bleeding were usually at a lower level than those found in normal animals. In four of the nine animals, death was produced by removing an amount of blood which varied from 0.8 to 1.6 per cent of the body weight. In at least two of the five remaining experiments the cardiac output and blood pressure were reduced much more than would have been anticipated had ether anesthesia been employed. The results of these experiments are given in table 2.

COMMENT

It has been stated by previous workers that spinal anesthesia causes a decline in blood pressure unless its administration is accompanied by the giving of a vasoconstrictor drug such as ephedrine or epinephrine. Burch and Harrison [2] have found that the output of the heart is also diminished, but the decline is usually not as relatively great as is the decline in blood pressure. In these experiments different dogs varied greatly as to the amount of blood loss which could be tolerated under spinal anesthesia. Two of the nine animals withstood a loss of blood amounting to approximately 3 per cent of the body weight without producing death. This difference is probably due to the fact that spinal anesthesia causes a greater reduction in blood pressure in some animals than in others. It has been noted that there is a great individual variation in the effects of spinal anesthesia on the blood pressure of patients.

Cattell [3] studied the effects of administering ether to dogs which had been bled from 15 to 20 per cent of the estimated blood volume and found that a decline in blood pressure usually resulted. It was thought that the decline in blood pressure was due to a reduction in the cardiac output. In other experiments, Cattell noted that ether administered after hemorrhage actually increased the blood pressure. Blalock [4] found that ether increases the output of the heart and causes very little alteration in the blood pressure. In the present experiments, comparison of the

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2. Burch, J. C., and Harrison, T. R.: The Effect of Spinal Anesthesia on the Cardiac Output, Arch. Surg. **21**:330 (Aug.) 1930.

3. Cattell, McKeen: Studies in Experimental Traumatic Shock: VI. The Action of Ether on the Circulation in Traumatic Shock, Arch. Surg. **6**:41 (Jan.) 1923.

4. Blalock, Alfred: Cardiac Output in the Dog During Ether Anesthesia: I. The Effect of Ether Anesthesia on the Cardiac Output, Arch. Surg. **14**:732 (March) 1927.

effects of hemorrhage during ether anesthesia with the effects of hemorrhage without anesthesia shows that there is very little difference between the two.

Spinal anesthesia is contraindicated in patients who have lost a great deal of blood or in patients in whom severe blood loss during the operation is anticipated. This precaution is important if the anesthesia is to extend high enough to produce a marked decline in blood pressure. Spinal anesthesia is especially indicated in patients who have diseases that are associated with an unusually large blood volume or in patients with a high blood pressure.

SUMMARY

In dogs, the danger of circulatory failure from hemorrhage is greater under spinal anesthesia than under ether anesthesia.

EVIDENCE SHOWN IN ROENTGENOGRAMS OF CHANGES IN THE VASCULAR TREE FOLLOWING EXPERIMENTAL SYMPATHETIC GANGLIONECTOMY*

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The constant changes that follow sympathetic ganglionectomy and ramisectomy have been attributed clinically to the increased flow of blood to the extremities, as shown by studies with the calorimeter and the thermocouple, but these conclusions have been based only on physiologic observations. In order to investigate the possibility of establishing an anatomic basis for the explanation of clinical results in such conditions as Raynaud's disease, thrombo-angiitis obliterans and polyarthritis, lumbar sympathetic ganglionectomy and ramisectomy was performed on animals.

Following operation, an opaque medium was injected into the arterial tree, and the arterial tree was then studied by means of the roentgen ray. In view of the fact that the animal on which the experiment could be conducted successfully must necessarily be one that could withstand an anesthetic and be of sufficient size to demonstrate any gross changes in the caliber of the vessels, dogs were chosen. In order that the conclusions should be absolutely unbiased, one of us (Craig) performed the operation, removing the sympathetic ganglions and severing the rami on one side only; this was done on three animals; then the other investigator (Horton) made the injections. Series of roentgenograms were made after each injection, and the plates were studied. As a check on the operative procedure, the lumbar sympathetic chain was dissected afterward.

EXPERIMENTAL WORK

On Jan. 18, 1929, three dogs were operated on under ether anesthesia. The surgical procedure was practically the same on all three. The technic of Adson, consisting of the transabdominal exposure of the lumbar sympathetic ganglions, was used. Because the ganglions proved to be farther apart in the dog than in man, only two ganglions, the second and third lumbar ganglions and connecting rami, were resected.

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In the first dog, the second and third lumbar ganglions on the left side were resected, and the lumbar ganglions on the right side were not disturbed. In the second dog, the second and third lumbar ganglions on the right side were resected, and the lumbar ganglions on the left side were not disturbed. In the third dog, the second and third lumbar ganglions on the left side were resected and the lumbar ganglions on the right side were not disturbed. The dogs were then allowed to recover and the injections were not carried out immediately, as we wished to observe the time element in connection with these procedures.

At intervals of twenty-eight, fifty-nine and one hundred and ten days after operation, under ether anesthesia the abdomens of the dogs were

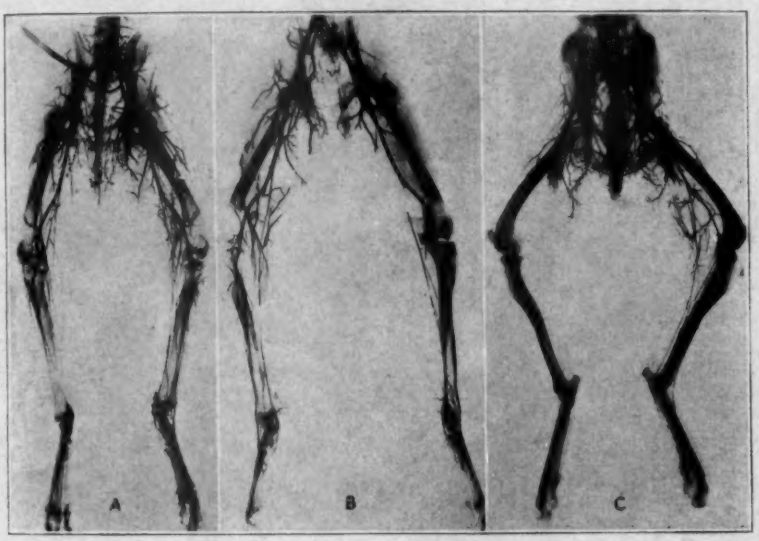

Fig. 1.—*A*, the second and third lumbar sympathetic ganglions on the left side were removed. Metallic mercury was injected into the arterial tree; a marked difference is shown in the appearance of the two extremities (first dog). *B*, the second and third lumbar sympathetic ganglions on the right side were removed. Metallic mercury was injected into the arterial tree. A slight but definite difference in the appearance of the two extremities may be noted (second dog). *C*, the second and third lumbar sympathetic ganglions on the left side were removed. Metallic mercury was injected into the arterial tree; a marked difference is shown in the appearance of the two extremities (third dog).

opened and a large-sized vessel was incised, allowing the animal to bleed to death. Immediately after death, the dogs were placed on the roentgen-ray table, and with a cannula in the abdominal aorta at the level of the first lumbar vertebra, metallic mercury was injected. Special care was taken to place the animal on the back in a horizontal posi-

tion, with the legs extended so that both knees were equidistant above the table. This enabled the pressure of the injection medium to be maintained at a constant level throughout the entire procedure. The mercury was allowed to flow into the aorta under its own weight, and the dogs were not disturbed until a series of stereoscopic plates had been exposed after varying quantities of mercury had been injected. Following the injection, sections of the arteries were taken for microscopic study.

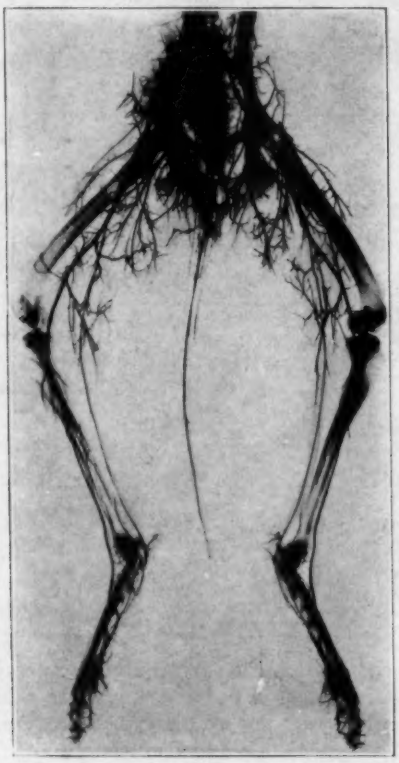

Fig. 2.—Periarterial sympathetic neurectomy was carried out on the left femoral artery, and mercury was injected into the arterial tree. The filling of the arterial tree in both lower extremities is uniform (fourth dog).

Since there has been some controversy in the literature regarding the relative efficacy of periarterial sympathetic neurectomy and lumbar sympathetic ganglionectomy and ramisectomy, another anatomic experiment was carried out to compare the results.

On May 16, 1929, periarterial sympathetic neurectomy was done on a dog, and the outer sheath of the left femoral artery was stripped for 5 cm. Twenty-two days later, the dog was killed and mercury injected into the arterial tree as in the other animals.

It is obvious that there is a definite change in the arterial tree in the extremity to which the sympathetic innervation had been interrupted by unilateral lumbar sympathetic ganglionectomy and ramisectomy (fig. 1). This change was not observed in unilateral periarterial sympathectomy, as evidenced by figure 2. When the pressure on the injection mass in the third dog in the series was increased (fig. 1 *c*), the injected material filled the arterial tree in both lower extremities (fig. 3). The same results were obtained in the first and second dogs.

Fig. 3.—Mercury injected into the arterial tree under 25 mm. of pressure (third dog).

SUMMARY

In dogs, definite evidences of vasodilatation in the arterial tree of the hind extremity were observed following interruption of sympathetic innervation by lumbar sympathetic ganglionectomy and ramisectomy. Changes were not observed in the arterial tree following periarterial sympathetic neurectomy. These observations are in accord with the clinical observations in man that have been made at the Mayo Clinic.

FORTY-SECOND REPORT OF PROGRESS IN ORTHOPEDIC SURGERY

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(Concluded from p. 554)

MISCELLANEOUS

Charcot's Arthropathy.—Wile and Butler [32] analyzed the records and physical observations in eighty-eight patients affected with Charcot's arthropathy, and came to the following conclusions:

The greatest age incidence was between 35 and 55 years. In the majority of cases the onset was gradual and insidious and extended over a period of months or years. The occasional sudden production of the condition was frequently the result of trauma bringing into visibility a preexisting subclinical process. The condition occurred three times more frequently in men than in women as compared with the incidence of tabes. Polyarticular involvement was common, no joint in the body being immune, but involvement of the knees and ankles occurred far more commonly than did any other form. Cerebrospinal syphilis was present in the majority of cases. Its absence, however, in typical cases indicated that it was not the essential primary etiologic factor. When present, the form of involvement was more commonly tabes. In the

32. Wile, U. J., and Butler, M. G.: A Critical Survey of Charcot's Arthropathy, J. A. M. A. **94**:1053 (April 5) 1930.

majority of cases the typical syndrome seemed to be an inactive or arrested cerebrospinal syphilis, few symptoms referable to the syphilis being ordinarily present. Subclinical insults, such as faulty posture and ataxia, played a larger rôle than did the actual trauma antedating the condition. The loss of the afferent nerve paths to the joint, rendering it unable to compensate for injury, seemed to be the ultimate etiologic factor.

Cystic Bursal Hygromas.—Jones [33] made a study of bursal hygromas, using the records and pathologic observations in fifty-five patients treated for this condition at the Mayo Clinic. He concluded that trauma, either severe or represented by a mild continued irritation, was the chief causal factor. He found no evidence to support the theory of infectious origin. The liquid contents of the cysts were partly of degenerative and partly of transudative origin.

Studies of the end-results were made in twenty-seven of the patients. In none had there been any recurrence following excision, which was the treatment advised. The author found a striking similarity between the bursal hygromas and carpal ganglions in their development.

Joint Complications in Smallpox.—Lombard [34] related two observations of joint sequelae in smallpox, the process in each case taking the form of osteo-arthritis. The first patient was a boy, aged 4 years, in whom during an illness with smallpox, swelling of the elbows developed, later followed by suppuration and complete bilateral ankylosis. The second patient presented multiple osteo-articular lesions consecutive to smallpox at the age of 2 years. The hand was deviated to the radial side as a result of destruction of the epiphyseal cartilage of the radius, and in addition there were lesions of the femoral condyles and of the lower end of the tibia. The infection had a tendency to localize in the juxta-epiphyseal regions and apparently had a great affinity for the radius.

Primary Bone Infection of Mycotic Origin.—Three instances of primary mycotic infection of the bones were reported by Meyer.[35] One patient was a boy, aged 12, with symmetrical foci in both os calces; the second was a youth, aged 19, with a lesion in the outer side of the os calcis. In both cases the organism was *Hemispora.* The third patient was a youth, aged 16, with a lesion in the upper end of the tibia caused by actinomycosis. In all the patients the first diagnosis had been tuberculosis, and general antituberculous treatment had been instituted without success. Local and general treatment with iodine seemed to have given good results.

33. Jones, H. T.: J. Bone & Joint Surg. **12**:46, 1930.
34. Lombard, P.: Rev. d'orthop. **16**:490, 1929.
35. Meyer, M.: Rev. d'orthop. **16**:624, 1929.

[Ed. Note.—Other authors have drawn attention to mycotic infection of bone, and it is evidently a condition to be borne in mind when puzzling lesions are encountered in the bones.]

Study of Joint Fluids.—Kling made a series of studies of joint fluids and reported the results in separate papers.

One investigation [36] dealt with the cytology of the fluid in traumatic effusion of the knee. By this means, Kling felt that he had been able to establish fairly conclusively the differential diagnosis between slight injuries to the joint without tear of important ligaments, more severe injuries with tearing of the semilunar cartilages or crucial ligaments and intra-articular fracture. The finding of erythroblasts and myelocytes, both products of bone-marrow, pointed to an intra-articular fracture. This diagnostic indication was verified in some instances when the roentgenograms were negative. When there were only ligamentous tears, fat, blood corpuscles and serum were present in the fluid, while with less severe injuries, such as bursitis and synovitis, only blood corpuscles and serum were found.

In another investigation Kling [37] applied the icterus index test of van den Bergh to effusions of the joint. The local formation of bilirubin raised the icterus index in traumatic hemorrhagic effusions above the level of the blood serum, while in inflammatory effusions the icteric index of the joint fluid was equal to or below the blood serum. In fractures of the joint the icterus index was unusually high. The author believed that this test, which is simple, might be helpful in the diagnosis of diseases of the joints.

In a third investigation, Kling [38] made a comparative study of the Wassermann reaction of the blood and the joint fluids in thirty-five patients. He found that the Wassermann test gave identical results in both the blood and the joint fluids, the joint effusions being chiefly of traumatic origin. The technic of the Wassermann reaction was the same in the joint fluids as in the blood, and he felt that both diagnostic and therapeutic considerations urged the application of the test to the joint fluid in every instance.

The Histologic Study of Normal and Diseased Bone.—Morrell [39] described a microtome knife that he had devised, made from an alloy of tungsten carbide and cobalt called "widia." With this knife he was able to cut sections varying from 6 to 12 microns in thickness from bone

36. Kling, D. H.: Am. J. Surg. **7**:824, 1929.

37. Kling, D. H.: Bilirubin in Effusions of Joints, Arch. Surg. **20**:17 (Jan.) 1930.

38. Kling, D. H.: Am. J. Syph. **13**:596, 1929.

39. Morrell, A. H.: Untreated Human Bone Sectioned with a New Knife, Arch. Path. **8**:816 (Nov.) 1929.

immediately after its removal during an operation and without any preliminary treatment. He believed that by the use of this knife the microscopic study and microchemical analysis of bone could be approached in a manner heretofore impossible and with greatly increased possibilities of success.

Jaffe [40] described methods of preparing bone for histologic study for every purpose, that were tried procedures. The choice of the method depended on the purpose of the examination. Unfortunately, there was no method of decalcifying bone that did not injure to a certain extent the cellular elements, the most essential part from the standpoint of a diagnosis. When decalcification was necessary, rapid treatment with nitric acid though not entirely satisfactory was the best procedure.

[ED. NOTE.—Jaffe's paper is of considerable value to orthopedic surgeons in helping to solve the troublesome technical problems that are always encountered when persons unfamiliar with bone sections are attempting to prepare them for histologic study. It is to be hoped that Morrell's new microtome knife will afford the means of avoiding cellular damage caused by decalcification, in which case it will represent a real step in progress.]

Muscular Atrophy Following the Use of Apparatus.—Basing his conclusions on the results of examination of children with congenital dislocations of the hip who had had their luxations reduced three years previously, Gaugele [41] pointed out that the criticism of the use of apparatus because it caused muscular atrophy was not substantiated by fact. Children who had been cured of congenital dislocations showed normal muscular development in spite of the fact that they had worn plaster splints and other apparatus for many months. On the other hand, children with untreated dislocations showed muscular atrophy of varying degrees. His experience in the treatment in scoliosis had convinced him that the wearing of supports prevented the severe progressive atrophy that was otherwise found in this condition. He had never seen evidence of damage to the internal organs from corsets or braces; on the contrary, their use often resulted in improved function.

Therapeutic Pools.—Lowman [42] expressed his belief that there was as much possibility for variation in exercises in an underwater gymnasium as in a regular gymnasium, with the added advantage that in the water the patient could be allowed to move in all planes whereas in the gymnasium, with the subject in the lying position, movements were

40. Jaffe, H. L.: Methods of Histologic Study of Normal and Diseased Bone, Arch. Path. **8**:817 (Nov.) 1929.

41. Gaugele, K.: Ztschr. f. orthop. Chir. **51**:74, 1929.

42. Lowman, C. L.: Physicial Equipment of Therapeutic Pools, J. A. M. A. **94**:845 (March 22) 1930.

restricted to certain planes. The successful use, however, of various types of apparatus depended on the resourcefulness of the technician and her knowledge of kinesiology, especially of pathologic or abnormal kinesiology as it existed in paralytic patients of those in whom joint plaster surgery or tendon transplantation has been done. The surgeon's understanding of how and when to prescribe the different types of work is also essential for the successful treatment in any case.

Operations on the Bones, Joints and Tendons; Anesthesia.—In an interesting and instructive article Koster and Kasman [43] discussed spinal anesthesia in the light of their experience with complete body anesthesia in 750 operative cases. They considered it perhaps the safest method of anesthesia and advocated its use not only in operations on the abdomen and lower extremities but also in operations on the chest, neck, head and upper extremities. They had no fear of respiratory embarrassment, and they had demonstrated in frogs and cats that application of the anesthetic directly to the medulla had no effect on respiration. They had never seen any adverse effect on the respiratory apparatus of man when anesthesia of the head and neck was obtained. They considered that the specific gravity of the injected solution had no effect in controlling the extent of diffusion of the drug. They insisted, however, that the degree of anesthesia depended directly on the amount of spinal fluid withdrawn before injection of the anesthetic, because the greater the amount of cerebrospinal fluid withdrawn, the greater would be the diffusion and therefore the higher the level of anesthesia. Decreases in blood pressure did not alarm them and they belittled the value of vasomotor stimulants. There were rarely serious complications from the use of spinal anesthesia, the chief ones being headache, diplopia, temporary paresthesia and urinary retention.

The greatest precaution taken by the authors was in the estimation of the proper dose of the drug. The details of this estimate were given, and the amount injected varied in proportion to the size and the age of the patient.

Francillon [44] recommended the use of local anesthesia in orthopedic operations. He expressed his belief that it possessed many advantages over general anesthesia. He had found the active muscular help of the patient of great importance in the transplantation of tendons, likewise in certain operations on the foot. He considered local anesthesia less dangerous than general anesthesia. In operations on the spine which necessitated the prone position of the patient, local anesthesia was especially advantageous as the difficulties and dangers in the use of general anesthesia in this position were much increased.

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43. Koster, H., and Kasman, L. P.: Surg. Gynec. Obst. **49**:618, 1929.

44. Francillon, M. R.: Ztschr. f. orthop. Chir. **53**:60, 1930.

Arthrodesis of the Shoulder.—A technic for arthrodesis of the shoulder with the aid of osteoperiosteal grafts was described by Key.[45] He had used it for tuberculosis and paralysis of the deltoid. He exposed the shoulder through the saber-cut incision, dividing the acromioclavicular joint and retracting the tip of the acromion with the attached deltoid outward. As complete synovectomy as possible was performed. The glenoid and the head of the humerus were denuded of cartilage, as was the under surface of the tip of the acromion. Two inch (5 cm.) osteoperiosteal grafts, which had previously been removed from the tibial surface, were then inserted subperiosteally between the glenoid and the head of the humerus. The arm was placed in 90 degrees of abduction and in about 25 degrees of anterior flexion. In tuberculous joints a nail was driven in through a stab incision, 3 inches (7.5 cm.) below the head of the humerus, directly through the head into the glenoid. A plaster casing made the day before operation was then applied, the arm being held in the desired position.

Stabilization of the Thumb.—Fitch [46] reported a method of arthrodesis of the first carpometacarpal articulation for paralysis of the opponens pollicis. The proximal end of the first metacarpal bone was first dislocated posteriorly. This produced a more advantageous functional position than when arthrodesis of the first metacarpal bone was made in normal relation to the greater multiangular bone (trapezium).

Combined Intra-Articular and Extra-Articular Fusion of the Tuberculous Hip.—Eikenbary and Le Cocq [47] devised a special technic for arthrodesis of the hip by a combined intra-articular and extra-articular method. A massive slab graft obtained from the ilium was fixed below in a split in the trochanter; above, it was in contact with the ilium, being anchored in place by a wire passed through the ilium from within the pelvis. They reported twenty-one cases in which the method had been employed with complete ankylosis of the hip and arrest of the disease in from six to twelve months postoperatively. They felt that extra-articular fusion alone was inadequate, as much tuberculous material was left in the joint which rendered the cure difficult. They did not consider draining sinuses a contraindication to operation.

[ED. NOTE.—Eikenbary and Le Cocq's method of fusion seems sound and the results in a small number of cases are impressive.]

Galland [48] advocated the bifurcation operation of Lorenz in selected cases of traumatic, pathologic or congenital dislocations of the hip; in nonunited fractures of the neck of the femur and in inflammatory

45. Key, J. A.: Surg. Gynec. Obst. **50**:468, 1930.
46. Fitch, R. R.: J. Bone & Joint Surg. **12**:190, 1930.
47. Eikenbary, C. F., and Le Cocq, J. F.: Northwest Med. **29**:23, 1930.
48. Galland, W. I.: Surg. Gynec. Obst. **50**:90, 1930.

processes involving the hip joint, such as arthritis deformans, tuberculosis or Charcot's disease. The advantages of the operation, according to Galland, were: It relieved pain, a good functional and cosmetic result could usually be obtained, the operation was relatively simple (although it had to be performed with the utmost care) and the period of recumbency after operation was short. The dangers were: injury to the femoral vessels by the distal fragment and nonunion. The author reported results in ten patients on whom the operation had been performed.

Reviewing the results of 103 operations on the hip joint that he had performed in the last twenty years, Ashhurst [49] stated that in his opinion the indications for typical arthroplasty had almost disappeared in the better development of the reconstruction operations of Whitman and Gill. He considered capsulorrhaphy a useful operation in paralytic dislocations of the hip. He had found reconstruction operations superior to bone pegging in fractures of the neck of the femur. Excision of the upper portion of the femur was indicated only as a life-saving measure, and in this case the author preferred Lambotte's incision. He found that the Smith-Petersen incision gave the best exposure for open reduction of the hip. Reconstruction operations had the widest field of usefulness in hip disabilities resulting from tuberculosis, pathologic dislocations, nonunion and chronic arthritis.

[Ed. Note.—Many orthopedic surgeons will question Ashhurst's statement as to the value of the reconstruction operation in tuberculosis of the hip.]

Osteochondritis Dissecans of the Ankle Joint.—Laewen [50] discussed osteochondritis of the ankle joint which he had encountered in four patients and operated on with good result. He considered that spontaneous cure might result either by actual restoration of the affected area or by complete disintegration of the necrotic piece of bone, but he thought that this was a rare occurrence.

Tarsal Autotransplants.—Curcio [51] reported two tarsal autotransplants for the correction of severe deformities of the feet. He performed a transverse section and in one instance removed the cuboid with a skin flap and inserted the bone and skin flap on the inner side of the foot in the space that was caused by correction of the deformity. In another instance the transplant consisted of the scaphoid and overlying skin; he inserted this in the wedge-shaped opening on the outer side of the foot made by correcting a valgus deformity.

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49. Ashhurst, A. P. C.: Operative Surgery of Hip Joint, Arch. Surg. **20**:87 (Jan.) 1930.

50. Laewen, A.: Zentralbl. f. Chir. **56**:2498, 1929.

51. Curcio, A.: Chir. d. org. di movimento **14**:216, 1929.

[ED. NOTE.—Curcio's autotransplantation of a portion of the tarsus with the overlying skin is of little practical value but it is interesting as it adds to the orthopedic surgeon's armamentarium for dealing with unusual conditions.]

Hallux Valgus.—Brandes [52] related his experiences with the operation for resection of the proximal two thirds of the first phalanx of the great toe for hallux valgus. He had performed this operation in more than 100 patients with good anatomic and functional results. He did not disturb any of the other structures of the foot except to remove with a chisel the prominent portion of the inner side of the head of the first metatarsal bone. After closure of the wound, he placed the toe in slight plantar flexion to avoid infolding and necrosis of the skin. He applied a plaster of paris foot plate, fixing the foot in slight plantar flexion and adduction. At the end of two weeks, he permitted the patient to walk with a metatarsal strapping.

[ED. NOTE.—The operation described by Brandes is the same as that devised by Keller in America many years ago except that it removes more of the proximal phalanx of the great toe than we would consider necessary.]

FRACTURES

Occupational Therapy.—Miss Taylor [53] discussed the value of occupational therapy in industrial injuries, and stated her opinion that a combination of physical therapy and occupational therapy achieved the greatest success in the treatment for industrial injuries as measured by the shortening of the period of disability. The occupational therapy ought to be carefully planned for the type of injury and the psychologic point of view of the patient. The injuries most commonly requiring treatment were those of the hand. With most of the conditions the greatest gain could be obtained if the treatment was begun in the first three weeks. The commonest disability was flexion, and the greatest danger was that of over-fatigue from too continuous contraction of muscles.

Fracture of the Capitellum of the Humerus.—In a report of three cases of fracture of the capitellum of the humerus, Ciaccia [54] emphasized the fact that this was a rare injury, only a few cases having been described in the literature. He had recognized two types: one in which there was displacement of the cartilage of the capitellum with a small section of the bone and one in which the fragment consisted of the capitellum and the outer lip of the trochlea. The treatment suggested was removal of the fragment which, according to the author, resulted in

52. Brandes, M.: Zentralbl. f. Chir. **56**:2434, 1920.
53. Taylor, M.: Occup. Therapy **8**:335, 1929.
54. Ciaccia, S.: Chir. d. org. di movimento **14**:181, 1929.

complete or nearly complete restoration of function. Lateral as well as anteroposterior roentgenograms were essential for studying the condition.

Compression Fractures of the Vertebrae.—Rogers [55] devised a frame for the correction of compression fracture of the vertebrae. It was essentially a Bradford frame, with flexible side pieces and a cross-bar, capable of being elevated, which could be moved to any point under the frame. The patient lay in the dorsal decubitus on the tight canvas cover and the spine was gradually hyperextended by cranking up the cross-piece; the correction of the fracture was gained by means of the action of gravity on the spine above and below. Maximum correction was usually obtained in about ten days. The patient could then be placed on a hyperextended Bradford frame where the correction was maintained for an additional eight weeks. This was followed by the use of an ambulatory plaster jacket for several months.

Dunlop and Parker [56] reported that they had corrected the deformity of vertebral compression fractures by a method of forcible hyperextension and that by this means they had obtained restoration of the normal form of the vertebrae in twenty-one patients. The patient was anesthetized and placed in the supine position, and folded sheets were passed across under the injured segment. Holding the ends of the sheets, the operator and his assistant suddenly made these taut, tossing the patient upward; at the same time, traction and countertraction were made by two persons pulling on the opposite ends of the patient's body. Following the reduction, care was taken to keep the body in a position of hyperextension, and a plaster jacket was applied with the aid of Goldthwait's frame.

Hempel [57] believed that he had found a way to avoid the dangers of forcible methods and at the same time to secure complete anatomic and functional restoration of the spinal column. He placed the patient on a hard, smooth mattress, at first in the supine position, but after a few days, in the prone position so that he could prop himself on his elbows. Boards were placed under the mattress to prevent sagging. As soon as the pain caused by the fracture had diminished, the muscles of the back were massaged and after seven weeks the patient was permitted to crawl on all fours as a regular exercise. Having become proficient in this exercise, the patient was next permitted to stand and finally to sit.

[Ed. Note.—Within the last two years great advances have been made in the treatment for compression fractures of the spine. Reduc-

55. Rogers, W. A.: Surg. Gynec. Obst. **50**:101, 1930.

56. Dunlop, J., and Parker, C. H.; Correction of Compressed Fracture of the Vertebrae, J. A. M. A. **94**:89 (Jan. 11) 1930.

57. Hempel, C.: Deutsche Ztschr. f. Chir. **223**:79, 1930.

tion of deformity is henceforth to be sought in this instance just as in other fractures. Several methods of reduction have been devised, beginning with the method of forcible reduction of Davis. Without personal experience of either the methods of Davis or those of Dunham and Parker, we would prefer the former to the latter as attended by less risk. Rogers' method of gradual hyperextension is the safest of all these methods as it entirely avoids the use of force. We have watched this method in use and can speak for its effectiveness. Whether the reduction accomplished by it is as complete as that obtained by the forcible methods will be decided in time. Hempel's method does not appear to us to be effective, nor is it logical to trust only to the muscles instead of to apparatus for protection. There is reason to hope that by the correction of deformity and by thorough and prolonged splinting to prevent recurrence of the deformity, the serious disabling effects of fractures of the vertebrae may be greatly diminished.]

Fractures of the Transverse Processes.—A study was made by Quaintance [58] of nonunion and disability in thirty-three patients with fractures of the transverse processes. In 85 per cent of the patients the fracture involved the second, third and fourth transverse processes. More than 50 per cent of the fractures were produced with the body in a position of acute flexion. Of a total of seventy-five fractures nonunion occured in 14, or in 18 per cent. In every instance of nonunion there had been wide separation of the fragments. None of the patients was permanently disabled, even with associated injuries of the pelvic bones, vertebrae and ribs which occurred in nine patients. The longest period of disability was seven months. Resection of the fractured transverse process was not necessary in any instance.

Fractures of the Pelvis.—Noland and Conwell [59] reported the treatment and results in a group of 125 patients with fractures of the pelvis. Only 39 of the patients had a single fracture of the pelvis. The fractures were divided into 3 groups: (1) single fractures in which the continuity of the weight-bearing ring was preserved; (2) multiple fractures in which it was necessary to relieve the bones of weight until the fracture was consolidated, and (3) the double vertical fracture (Malgaigne's fracture) usually accompanied by extensive dislocation of the whole pelvis. The anterior ring fractures and marginal fractures gave the best results. Fractures of the acetabulum yielded fair results, but in the fractures involving the posterior ring about the sacro-iliac joint the poorest results were obtained, disability ranging from 25 per

58. Quaintance, P. A.: Fracture of the Lumbar Processes of the Transverse Vertebrae, Arch. Surg. **10**:968 (Dec.) 1930.

59. Noland, L., and Conwell, H. E.: Acute Fractures of the Pelvis, J. A. M. A. **94**:174 (Jan. 18) 1930.

cent to almost permanent total disability. When discharged, only about 60 per cent of the patients had what was called good anatomic position, but the authors were sure from their observations that excellent functional results were frequently obtained in cases in which good anatomic position was by no means secured. Open reduction for correction of displacement of bony fragments was done in only two instances, and then only to relieve pressure of the displaced fragments on the rectum and bladder. The authors were of the opinion that what appeared to be a poor position of the fragments was by no means a constant cause of persistent pain and disability. The average number of days lost from work in both industrial and civilian cases was 175. It was noticeable that the majority of civilian patients returned to their work much earlier than did the industrial patients.

Fractures of the Neck of the Femur.—Hey-Groves [60] reviewed the results in 24 of his own cases and in 116 other cases of fractures of the neck of the femur reported from three large English hospitals. In the latter group he found nonunion in 23 per cent and poor or bad results in 53.3 per cent of cases. He concluded that patients with basal fractures might be treated successfully either by traction or by the Whitman abduction method, traction probably being better as it permitted earlier motion of the hip. In true intrascapular fractures treatment involved a choice between the Whitman abduction method and the pegging operation. For young and vigorous persons, the author preferred pegging, i. e., the insertion of a beef bone peg in a hole bored through the proximal fragment into the trochanter. In other patients in whom the Whitman method was used, pegging could be resorted to if roentgenograms showed nonunion at the end of three months. When operation revealed that the proximal fragment had lost its cartilage and that the bone was soft and friable, it was much better to remove the head and perform a reconstruction operation.

Albee [61] wrote enthusiastically of the results of treatment for nonunited fractures of the neck of the femur by the operative insertion of autogenous bone pegs. Thirty-six patients had been treated in this manner. For the treatment in fresh fractures of the neck of the femur, he did not believe that the Whitman procedure could be improved on; in cases of delayed union or nonunion, however, he preferred the bone peg operation or reconstruction procedure. In the bone peg operation he used two incisions: The peg was made from a tibial graft and driven in through a drill hole made from a point just below the greater trochanter through the neck into the femoral head. He stated that over 90 per cent of the patients so treated had obtained union. He was

60. Hey-Groves, E. W.: J. Bone & Joint Surg. **12**:1, 1930.

61. Albee, F. H.: Surg. Gynec. Obst. **49**:810, 1929.

opposed to the use of nails or other material for the fixation of the fragments. The choice between the bone peg operation and the reconstruction operation depended on the cooperation of the patient, the duration of the fracture and the condition of the fragments at the time of operation. Often the decision could not be made until operation, when the fragments were actually exposed.

Fractures of the Bones of the Foot Other Than the Os Calcis.—In considering fractures of the bones of the foot other than the os calcis, Brown and Brown [62] made the following grouping in relation to their importance to function: (1) fractures of the astragalus, (2) fractures of the inner tarsals which, with the first, second and third metatarsals, constituted the longitudinal arch, (3) fractures of the fourth metatarsal, (4) fractures of the fifth metatarsal and (5) fractures of the phalanges and sesamoids.

In a group of forty-six fractures of bones of the foot excluding the os calcis there were twenty-eight single and eighteen multiple fractures. The incidence was about the same for fractures of the metatarsals except for the fourth metatarsal which was smallest. There was one fracture of the astragalus, one of the cuneiform and two of the sesamoids. The average loss of time for a fracture of the metatarsal was forty-six days and for a fracture of the phalanx thirty-three days.

DISLOCATIONS

Dislocation of the Cervical Vertebrae.—From an experience with seventeen bilateral cervical dislocations and thirteen unilateral dislocations Langworthy [63] believed that reduction by the method of Walton should be tried in all cases provided that the roentgenograms showed no evidence of fracture or disease. To be sure of preventing redislocation, which may occur as late as ten days after reduction, a plaster casing should be applied.

All the patients with unilateral dislocations showed complete recovery from symptoms. Five of the patients with bilateral dislocations died, and five of eight patients showed serious injury to the spinal cord.

Old Dislocations of the Shoulder.—Key [64] presented the histories of two cases of old dislocation of the shoulder, both of the subcoracoid type. He stated as a general rule that dislocations of eight weeks' duration or less could be reduced by manipulation while dislocations of twelve weeks' duration or more required open operation. In manipula-

62. Brown, W. L., and Brown, C. P.: Fractures of the Bones of the Foot Other Than the Os Calcis, J. A. M. A. **94**:461 (Feb. 15) 1930.

63. Langworthy, M.: Dislocation of Cervical Vertebrae, J. A. M. A. **94**: 86 (Jan. 11) 1930.

64. Key, J. A.: Missouri State M. A. J. **27**:129, 1930.

tion, great care had to be exercised not to rupture the axillary artery or the brachial plexus or fracture the humerus. When the head of the humerus was brought to the anterior border of the glenoid, and the arm was immobilized with the hand on the opposite shoulder, spontaneous reduction often occurred.

Chronic Recurring Temporomaxillary Subluxation. — Morris [65] described carefully the intricate anatomy of the temporomandibular joint and discussed the mechanics and pathology of "snapping jaw." He advised operative correction of this condition rather than the use of external or intra-oral splints, such as had been advocated by some writers. Two operative procedures were suggested: (1) Nieder's operation which consisted of turning down a flap of temporal fascia and sewing the end to the capsule of the joint so as to limit the excursion of the condylar head, and (2) the procedure employed by Morris in which the condylar head was scarified and a series of reefing stitches was placed in the capsule.

Habitual Dislocation of the Patella.—Blencke [66] discussed the various operations for the correction of habitual dislocation of the patella and stated that during recent years he had used a modification of the operation described by Drehmann. This consisted of transplanting the insertion of the gracilis muscle into the outer border of the patella. The patella was displaced inward as much as possible, and the tendon was fixed subperiosteally under moderate tension. The leg was placed in splints for three weeks, after which exercise and massage were begun. After four weeks the patient was permitted to walk, and a week later he was allowed to leave the hospital wearing an elastic knee-cap. All of the patients on whom the operation had been performed remained free from recurrence, in spite of the fact that one sustained a severe traumatism to the leg five years after operation.

AMPUTATIONS

The Healing of Amputated Bones.—Barber [67] studied the amputation stumps in forty skeletons, and observed the successive changes that took place in the process of healing and repair of the end of the bone. Briefly, these changes were found to be comparable to those of healing fractures. These in order were: (1) vascular erosion of the end of the bone and the adjacent shaft, (2) macular disintegration of the bone adjoining the site of amputation, (3) rounding of the bony stump, (4) closure of the medullary cavity by a cap of bone which rapidly became condensed and (5) restrained production or absence of osteophytes.

65. Morris, J. H.: Surg. Gynec. Obst. **50**:483, 1930.
66. Blencke, B.: Zentralbl. f. Chir. **57**:1159, 1930.
67. Barber, C. G.: Ann. Surg. **90**:985, 1929.

The formation of the osteophyte on the femur was usually harmful, whereas on the tibia or the fibula it frequently caused union between the two and was to be desired.

RESEARCH

The Bacteriology of Normal Bone.—Santos [68] made bacteriologic studies of twenty-four specimens of bone and marrow obtained from persons without bone lesions and of twenty-four samples of bone obtained from apparently healthy dogs. No organisms were recovered from any of these samples. The author considered that this was corroborative evidence that the streptococci and staphylococci that had previously been reported as recovered at times from solitary bone cysts were causally related to these bone lesions.

The Stimulation of Bone Growth by Venous Stasis.—The effect of venous stasis on the growth of bone as indicated by the healing of fractures was studied experimentally by Pearse and Morton.[69] In twelve dogs, portions of the fibula of identical size were removed subperiosteally from both legs. On one side the popliteal vein which received the drainage from the fibula was ligated just distal to its confluence with the femoral vein while the other leg was used for control purposes. The repair of the bony gap was observed by periodic roentgenograms. It was found that the union was accelerated on the ligated side in every case except one in which an interposition of muscle had occurred. In two patients who showed markedly delayed union of fractures, callous formation occurred promptly after the induction of intermittent venous stasis with a blood pressure cuff inflated a little above the level of diastolic pressure.

The Effect and Mode of Action of Vitamin D.—Bauer and Marble [70] offered experimental evidence that the action of viosterol was to increase the absorption of calcium from the gastro-intestinal tract. They fed twelve cats on a diet deficient in calcium over a period long enough to reduce markedly the trabeculae in the bones. They then amputated the left fore leg of each cat. The animals were then placed on a high calcium diet, and six of the twelve cats were given viosterol. The animals were killed in pairs (one which had been given viosterol and one which had not). At varying lengths of time the humerus of each animal was studied. The humeri of the cats receiving viosterol showed a much greater increase in bone trabeculae than did the controls. Bauer and Marble were able to duplicate these observations with their clinical patients, as evidenced by complete calcium metabolism studies.

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68. Santos, J. V.: J. Bone & Joint Surg. **12**:150, 1930.

69. Pearse, H. E., and Morton, J. J.: J. Bone & Joint Surg. **12**:97, 1930.

70. Bauer, W., and Marble, A.: New England J. Med. **201**:809, 1929.

From experiments on guinea-pigs, Roi [71] believed that the administration of viosterol accelerates the processes of repair and the consolidation of the callus. He considered that the varying results obtained in experimental work depend on the type of irradiation used.

Brougher [72] studied the effect on the blood coagulation time of cod liver oil or viosterol in fourteen patients who showed a marked lowering of the blood coagulation time owing to various diseases. Viosterol was given in 10 drop doses and cod liver oil in doses of 30 cc. Four hours after cod liver oil or viosterol had been given, the clotting time was determined. In all instances it was found to be normal.

The Influence of the Withdrawal of Blood on the Healing of Fractures.—Rallo [73] made a study of the influence of withdrawals of blood on the healing of fractures in rabbits. He found that periodic removals of a considerable quantity of blood resulted in an acceleration of the repair of fractures and increased the capacity for fixation of lime salts in all the tissues that were destined for this fixation.

The Study of Semilunar Cartilages.—Tobler [74] made an examination of 400 semilunar cartilages obtained from 100 cadavers varying in age from infancy to old age. Beginning with the second decade, he found regularly evidences of different types of degeneration of the cartilages. Fatty degeneration was the most common, being found in 67 per cent, and mucous degeneration was noted in 15 per cent. After the thirty-seventh year all of the cartilages were found to show some signs of mucous degeneration. Almost as frequent as the mucous degeneration was what the author called asbestos-like degeneration. Incrustation of the degenerated areas with lime salts was seen in 25 per cent of all cases. The author considered the poor circulation of the semilunar cartilages responsible for the tendency to degeneration.

71. Roi, G.: Riforma med. **45**:1551, 1929.
72. Brougher, J. C.: Northwest Med. **29**:38, 1930.
73. Rallo, A.: Riforma med. **45**:1345, 1929.
74. Tobler, T.: Schweiz. med. Wchnschr. **59**:1359, 1929.